KINEMATIC CHANGES FOLLOWING ROBOTIC-ASSISTED UPPER EXTREMITY REHABILITATION IN CHILDREN WITH HEMIPLEGIA: DOSAGE EFFECTS ON MOVEMENT TIME

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Kinematic Changes following Robotic-Assisted Extremity Rehabilitation in Children with Hemiplegia: Dosage Effects on Movement Time

Background: Rehabilitation Robotics (RR) has become a more widely used and better understood treatment intervention and research tool in the last 15 years. Traditional research involves pre and post-test outcomes, making it difficult to analyze changes in behavior during the treatment process. Harnessing kinematics captured throughout each treatment allows motor learning to be quantified and questions of application and dosing to be answered.

Objective: The aims of this secondary analysis were: (i) to investigate the impact of treatment presentation during RR on upper extremity movement time (mt) in children with hemiplegic cerebral palsy (CP) and (ii) to investigate the impact of training structure (dose and intensity) on mt in children with CP participating in RR.

Methods: Subjects completed 16 intervention sessions of RR (2 x week; 8 weeks) with a total of 1,024 repetitions of movement per session and three assessments: pre, post and 6 month f/u. During each assessment and intervention, subjects completed "one-way record" assessments tracking performance on a planar task without robotic assistance. Kinematics from these records were extracted to assess subject performance over the course of and within sessions.

Results: For all participants, a significant decrease in mt was found at post-test and follow-up. No significant differences were found in mt for age, severity or group placement. A significant interaction was found between treatment day, block and group ($p = .033$). Significant mt differences were found between the three blocks of intervention within individual days (*p* = .001). Specifically, significant differences were found over the last block of treatment (*p* = .032) and between successive treatment days (*p* = .001).

Conclusion: The results indicate that for children with CP participating in RR, the number of repetitions per session is important. We hypothesized that children's performance would plateau during a treatment day as attention waned, the opposite proved to be true. Despite the high-number of repetitions and associated cognitive demand, subjects' performance actually trended upwards throughout the 1,024 repetitions suggesting that children were able to tolerate and learn from a high volume of repetitions.

Peter Altenburger, PhD, PT, Chair

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Chapter 1 : Background

Introduction

Neuroplasticity (cortical reorganization) is a construct that describes the human brain's ability to adapt and reorganize when exposed to adequate stimuli.[1] Throughout life, neuroplasticity is demonstrated through growth and development. Every new skill mastered and knowledge learned is evidence of the human brain's ability to adapt in the presence of new information and demands.[1-3] Following neurological impairment, whether from a developmental or injury origin, neuroplasticity is a key component of recovery.[3,4] Acknowledging that any brain is plastic, even one injured or affected by disorder, offers new opportunities within rehabilitation to restore function lost to injury.

Previous and current approaches to rehabilitation for individuals with a motor impairment, developmental or acquired, have focused primarily on improving function within the constraints of functional limitations. In practice, therapists work with a patient to improve limitations (such as increasing strength or improving range of motion), but with an implied acceptance that the patient will ultimately improve function through modification of activity and use of adaptive equipment.[4] Whether this modification materializes as an assistive walker, orthotics, or compromised movement strategy, our historical acceptance that neurological injuries are static, or, at the very least, unable to completely repair, have guided decision making in determining a patient's ultimate functional recovery.[5,6] With an increased understanding of neuroplasticity and its impact post-injury, the field of rehabilitation has begun to accept that neurological damage may be reversible due to cortical reorganization, at least in its functional presentation, leading to new approaches in treatment and increased expectations for patient recovery.[4]

In order to achieve cortical reorganization following injury, the appropriate amount of practice, i.e. motor learning, must be achieved.[7] In uninjured persons, motor learning occurs through practice; consolidation of new skills occurs through repeated exposure and mastery.[8,9] During physical rehabilitation, motor learning occurs through specific interventions designed to maximize a patient's exposure to a lost skill or ability. Rehabilitative therapists utilize the concepts of the motor learning theory to expose patients to the practice necessary to improve function. Among the components of the motor learning theory are the constructs of repetition, intensity, and specificity[4]. When applied appropriately, these concepts can facilitate cortical reorganization, or neuroplasticity, with the ultimate goal of a translation into improved functional skill. Through proper practice, the injured brain possesses the potential to reorganize itself so that uninjured areas of the motor cortex begin to assume the responsibilities of damaged portions.[10] Through this, patients can recover skills lost as the result of injury, rather than developing compensation strategies that consist of abnormal movement patterns.

Robotic-assisted therapy offers a medium in which the constructs of the motor learning theory can be applied in a very specific and controlled manner.[11] Robotic-assisted therapy involves the use of a computer driven orthoses to modulate components of human movement during rehabilitative tasks.[12,13] With robotic-assisted therapies, rehabilitation therapists are able to create intervention protocols that capitalize on the principles of motor learning, namely: repetition, intensity and specificity.[14] Within a robotic intervention, patients may participate in up to 1,000 repetitions or more of a specific movement in a single intervention session. Grouped over several sessions, this massed repetition can potentially provide the stimulus necessary to invoke changes within the motor cortex and create lasting change. Through this, patients can begin to practice functional tasks and recover independence previously lost due to injury or disorder; or, in the case of developmental disorders, develop skills that have yet to be learned.

Much of the research conducted in robotic-assisted rehabilitation to date has focused predominantly on the adult post-stroke population. Mounting evidence suggests that robotic intervention is an appropriate treatment option for adults who have experienced a decrease in functional ability following a stroke.[11,13,15-25] Cerebral Palsy (CP) is a childhood disorder that manifests itself in ways similar to that of a stroke in an adult. CP results from injury to a developing brain prior to, during, or immediately after birth.[26,27] Children with CP suffer from impairments including abnormal tone, decreased strength, poor motor control and abnormal muscle synergies.[27] As in the adult stroke population, robotic rehabilitation offers a promising treatment platform to expose children to the amount of consistent practice necessary to induce cortical reorganization, thus improving motor function. Early results have supported this claim, yet many questions remain as to the proper application of this intervention in the CP population.[28]

In considering robotic rehabilitation for the CP population in the context of previously conducted research, one of the predominate questions is dosing: How much, and how often, is an adequate dose of robotic intervention to impart meaningful and lasting changes in children with CP? Intuitively, robotic-based interventions offer advantages over traditional therapies in their ability to provide massed repetition and consistency within practice repetitions. Current limitations of robotic-assisted therapies exist in their lack of carry-over to real world tasks, i.e. activities of daily living such as dressing and feeding. Acknowledging this, robotic-assisted therapies are not a replacement for traditional approaches; rather, they are a potentially powerful adjunct to improve outcomes from traditional approaches, speed recovery times, and increase therapist efficiency. However, for these combined benefits to be realized, questions regarding robotic-assisted therapies must first be answered so that they can be applied correctly to varying populations with varying goals.

Purpose of Study

This study was designed to examine the effects of task-specific, upper-extremity robotic rehabilitation using the MIT-MANUS robot in a pediatric population with a diagnosis of hemiplegic CP. While clinical outcome results from this study have been published,[29] this secondary analysis is examining kinematic values, specifically movement time, as a measure of functional improvement. An inherent benefit of robotics in rehabilitation is the ability to record specific and constant data relative to a patient's performance,[30] allowing researchers to more critically assess responses to an intervention. From this kinematic data, this study attempts to answer questions related to dosing (number of optimal treatment sessions of robotic rehabilitation) and intensity (number of optimal repetitions within a treatment session of robotic rehabilitation).

Significance of Study

Limited research exists for robotic rehabilitation in the pediatric population. The results of available literature are primarily limited to clinical outcome measures, which may not be sensitive enough to capture performance changes following robotic intervention,[31] and/or may not be appropriate in capturing the expected outcomes.[29] Within the pediatric population, only cursory looks at kinematic outcomes exist,[31] though a study utilizing the MIT-MANUS in an adult stroke population has demonstrated kinematic changes related to robotic training.[30]

The results of this study may provide an improved understanding of a child's response to robotic rehabilitation. Further, this study answers questions regarding dosing and intensity that can be beneficial in the design of future studies examining robotic-assisted rehabilitation as well as globally to non-robotic studies examining interventions targeting motor learning in a pediatric CP population.

To this end, this dissertation proposes a conceptual framework of *Rehab Effort* around the construct that "more is better"[32] (Figure 1.1) regarding repetitions during motor recovery. As in human development and normal motor learning, where increased repetitions lead to improve consolidation of skills[8,33], it is also true in neurological recovery: increased repetitions, or practice, can lead to improved function.[34] Research has been conducted exploring the concept of dosing within rehabilitation protocols[35,36], with no concrete determinate of an ideal strategy. Through this framework of rehab effort, we are suggesting that perhaps the more critical component is amount of total practice, with the scheduling arrangement of that practice being less important. The implication of this framework is simple: more repetitions equals more effort.

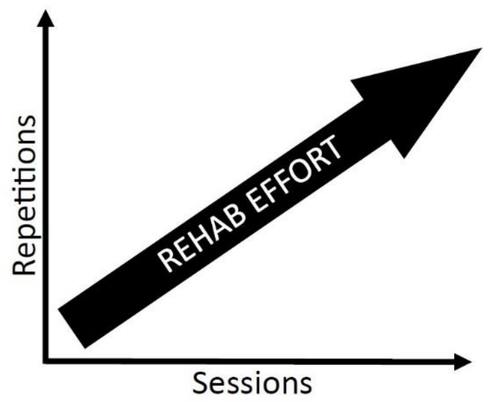

Figure 1.1: Rehab Effort Conceptual Framework

Specifically, rehab effort is being presented as a conceptual framework of dosing with cumulative additions of repetitions over time occurring within treatment sessions and/or over the course of successive treatment sessions. Whereas dosing typically describes the structure or application of rehabilitation interventions within a given session or how sessions are scheduled in a given sequence, rehab effort focuses on the total effort within an entire duration of an intervention. (Figure 1.2)

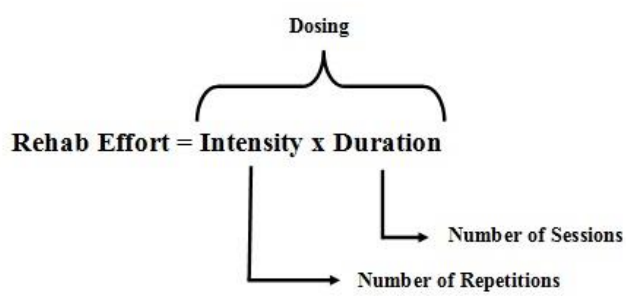

Figure 1.2: Rehab Effort as a product of Dosing

Study Aims

Aim 1**:** To investigate the impact of treatment presentation and application during robotic-assisted training on upper extremity movement time in children with hemiplegic CP.

The initial aim of this secondary analysis is to further investigate the questions posed in the original clinical study. Where the original study only utilized functional outcomes, this secondary analysis utilizes kinematic data to provide more context to the questions asked. Aim 1 is an attempt to validate the findings from the original study through kinematic data, or to discover changes that were previously unrealized because of limitations of the testing battery that was utilized.

Hypotheses*:* 1) Robotic-assisted training will decrease upper extremity movement time in children with hemiplegic CP. 2) Children participating in random training will increase movement times more than those participating in blocked training. 3) Children who are considered "less severe" at study intake (higher Fugl-Meyer scores) will increase movement times more than children who are "more severe" (lower Fugl-Meyer scores). 4) Children's age will not affect changes in movement time following robotic-assisted training, regardless of group.

Research Question 1.1: Does task-specific, upper extremity robotic-assisted rehabilitation with targets delivered in a random presentation decrease movement time more than a blocked presentation in children with hemiplegic CP?

Analysis: A 2-way repeated measures ANOVA with a within subjects effect for time (Pre, post, follow-up) and a between subjects effect for group (random vs blocked). Post-hoc analysis included pairwise comparisons with a Bonferroni correction applied.

Research Question 1.2 and 1.3: Does age affect movement time during upper extremity robotic-assisted rehabilitation delivered in both random and blocked presentations in children with hemiplegic CP? Does severity at intake affect movement time during upper extremity robotic-assisted rehabilitation delivered in both random and blocked presentation in children with hemiplegic CP?

Analysis: An ANOVA with a within subjects effect for time (pre, post) and with age and severity as random factors was calculated; the interactions (time by age and time by severity) were of interest.

Aim 2**:** To investigate the impact of training structure (dose and intensity) on upper extremity movement time in children with hemiplegic CP participating in upper extremity, task-specific robotic-assisted rehabilitation.

The secondary aim of this secondary analysis is to utilize the kinematic data collected in real-time during robotic treatment sessions to explore the changes in movement time that occurred both within each individual treatment day and over the course of each individual treatment session. Rather than utilizing only pre-test and post-test data to evaluate the overall change related to an intervention, the collected kinematic data allows us to begin to explore questions of dosing as a more focused level.

Hypothesis*:* Dosing (number of treatment days), intensity (number of repetitions per treatment day, i.e. treatment block) and target presentation (treatment group: blocked vs random presentation) will have an effect on movement time changes in children with hemiplegic CP participating in task-specific, upper extremity robotic-assisted rehabilitation.

Research Question 2: Do movement time changes in children with hemiplegic CP participating in robotic rehabilitation demonstrate an interaction between treatment day, treatment block, and/or treatment group to suggest an effect of dosing and intensity on outcomes?

Analysis: A univariate ANCOVA was run on the block difference data with treatment day, block, and group as fixed factors, and age and severity as covariates. Post-hoc tests outlined below were calculated to investigate the treatment day by block by group interaction.

Research Question 2.1: Do improvements in movement time over individual treatment days differ across the course of 16 treatment days suggesting an effect of dosing on improvements in children with hemiplegic CP participating in upper extremity robotic rehabilitation?

Analysis: A univariate ANCOVA was run on the block difference data with treatment day as a fixed factor, and age and severity as covariates. Pair-wise comparisons were computed to determine differences between treatment days.

Research Question 2.2: Is there a significant difference in movement time changes over each block of treatment during the course of 16 robotic-assisted training days suggesting an impact of intensity in children with hemiplegic CP?

Analysis: A univariate ANCOVA was run on the block difference data with block as a fixed factor, and age and severity as covariates. Pair-wise comparisons were computed to determine differences between blocks of treatment.

Research Question 2.3: Does the change in movement time improvements, each day, over the course of 16 treatment sessions of upper extremity robotic rehabilitation differ between those children assigned to a random presentation group and those assigned to a blocked presentation group?

Analysis: A univariate ANCOVA was run on the block difference data with group and block as a fixed factors, and age and severity as covariates. Pair-wise comparisons were computed to determine differences between groups.

Assumptions

Assumptions were made specific to the following: 1) Participants were accurately diagnosed by their respective physicians as having hemiplegic CP or acquired brain injury, 2) Participant performance during evaluation sessions was reflective of maximal effort, 3) Participants were fully engaged during training sessions and that, when robotic metrics indicated otherwise, verbal motivation and instruction by the researcher was sufficient in re-directing the child to task.

Limitations

This study is potentially compromised by a small sample size (*n* = 21 subjects enrolled in study). Although subjects were initially well distributed amongst gender (males, 12; females, 9), age (4-11), and group assignment (random, 12; sequential, 9); 5 subjects were lost at follow-up decreasing group distributions and further limiting sample size.

One of the primary points of investigation within this study was the presentation of targets during intervention sessions. Subjects were randomly assigned to a random presentation or a sequential presentation. The random presentation of targets is intended to mimic motor learning theories suggesting that randomness produces a beneficial effect in the acquisition of motor skills[37]. However, as it will be discussed in Chapter 5, there are questions to consider as to whether the random presentation of targets provided within this intervention (utilizing the MIT-MANUS) contained enough variability to accurately be considered random.[29]

Definition of Terms

1. *Neuroplasticity*: The collective processes by which the brain is remodeled in response to adequate stimuli. Neuroplasticity occurs in both the healthy brain, as learning, and the injured brain, as recovery.[1]

2. *Motor Learning*: A term encompassing motor adaptation, skill acquisition and decision making that contribute to the attainment and consolidation of skill following exposure to stimuli in both healthy and injured populations.[38]

3. *Cerebral Palsy*: A group of non-progressive, permanent disorders of the development of movement and posture in the developing brain, resulting in a broad spectrum of clinical symptoms including, but not limited to: poor muscle control, abnormal posture, abnormal muscle synergies, abnormal muscle tone and resulting secondary sequelae.[26,27]

4. *Stroke*: An impairment caused by abnormal blood flow to areas of the brain resulting in neurological symptoms of weakness, motor control abnormalities, and spasticity among others.[39]

5. *Robotic-Assisted Rehabilitation*: A modality utilizing a computer-controlled, human/machine interface to provide non-fatigable, repetitive and consistent practice for patients' recovery from neurological impairment or injury.[12,13]

6. *MIT-MANUS (InMotion2):* An upper-extremity robotic rehabilitation device that assists rehabilitation through a graded training sequence of planar reaching movements that patients perform through an end-effector robot.[40]

7. *Movement Time*: In this study, movement time is designated as the key outcome variable and is defined as the amount of time, in seconds, that a participant moves the robotic cursor of the MIT-MANUS robot from the center target to one of the eight peripheral targets.

8. *Rehab Effort*: In this study, Rehab Effort is being presented as a theoretical measure of dosing with cumulative additions of repetitions over time occurring within treatment sessions and over the course of successive treatment sessions.

Chapter 2 : Review of the Literature

Introduction

The research literature has a significant amount of published studies investigating the merits of robotic technology as a viable treatment intervention for neurological recovery.[11-15,29,30] At the foundation of this approach is the idea that the brain and central nervous system are adaptable during both normal and abnormal development, as well as following injury.[2,4] Looking more specifically within the robotic literature, evidence exists for upper extremity application relative to neuroplasticity in the recovery model of adults with neurological deficits.[11,19-22,41] Although much less evidence exists to support robotic application for children with hemiplegic cerebral palsy (CP); that which does is positive.[29,31,42-45] What is most evident is that a significant gap in evidence exists to support both the application of and appropriate dosing for robotic interventions in the pediatric population. This chapter reviews the neuroplasticity literature, provides a foundation for the efficacy of robotic intervention, and defines what is known and unknown regarding its application to the pediatric rehabilitation environment.

Neuroplasticity

The term "plasticity" was first used to describe the nervous system by William James in 1890, stating: "Plasticity, then, in the wide sense of the word, means the possession of a structure weak enough to yield to an influence, but strong enough not to yield all at once. Organic matter, especially nervous tissue, seems endowed with a very extraordinary degree of plasticity". [46] The processes by which the brain is remodeled are collectively referred to as neuroplasticity.[1] Various mechanisms, comprising processes of both normal development and brain activity, as well as processes associated with injury and disease are included under the umbrella term neuroplasticty.[2,3] These mechanisms include the formation of new neurons and glial cells (neurogenesis), as well as the formation of new connections and alterations in existing pathways. Additional changes occur through synapse formation and elimination, dendritic remodeling, axonal sprouting, and pruning.[1] Collectively, neuroplasticity aids in our development from embryo to adult, allowing us to learn new information, consolidate memories, and acquire new motor skills. Although James' original working definition is now well over 100 years old, we continue to find evidence supporting his premise; that the brain continuously reorganizes to encode new experiences, thus enabling behavioral change. [8,9] Within an injured nervous system, driving recovery through behavioral, cognitive, and sensory experiences,[4] enables researchers and clinicians alike to identify rehabilitation strategies targeted at improving function lost because of neurological impairment.[3] Reorganization of the damaged brain is achieved by promoting the endogenous process that occurs during healthy neuroplastic changes.[4] In order for one to appreciate these changes manifested during a recovery phase, it is important to first understand the neuroplastic process that occurs during normal development.

Development and Anatomy

In the first 24 weeks of gestation, the brain undergoes complex morphological changes, including the formation of the cerebral hemispheres, folding of the cortex, and shaping of the ventricular system.[47] During normal development, cortico-spinal motor projections sprout from the motor cortex and grow in a cortico-fugal manner, reaching the spinal cord by 20 weeks gestation. During this process, each hemisphere develops bilateral projections resulting in a situation of competition between ipsilateral and contralateral projections to motor neurons in the spinal cord. Continuing normal development is characterized by a gradual weakening of ipsilateral projections and strengthening of contralateral projections.[48] Experimental data from macaque monkeys suggest that this process is part of an overall elimination of cortico-spinal axons, most of which never synapse onto spinal neurons.[49] Additionally, evidence from a neonatal cat model suggests that ipsilateral weakening and contralateral strengthening of cortico-spinal motor projections, also known as competitive withdrawal,[48] is driven by neuronal activity[50] related to input crucial to the development of the sensorimotor system.[51] However, in both typical and atypical development, a portion of ipsilateral projections do terminate on motor neurons in the spinal cord preserving some degree of motor control from the ipsilateral hemisphere.[51]

Occurring in parallel with the development of the cortical-spinal tracts is the development and differentiation of the cotex.[47] The motor cortex is divided into the primary motor cortex (M1), the pre-motor cortex (PM), the cingulated motor area (CMA), and the supplementary motor area (SMA).[52] Traditional theory of the homunculus has described a cortex with a general global segregation of body parts, (Figure 2.1) evident in functional maps of M1.[53] Although generally true, it is now recognized that the representations of individual movements are widely distributed and overlapping within the motor cortex.[54,55] A mosaic-like pattern of the representation of individual digits, wrist, forearm, elbow and shoulder has been described in animal models, with no clear arrangement of movements represented within M1,[10,56-58] findings that have been repeated in human subjects through transcranial magnetic stimulation.[59] Additionally, these complex areas of representation are densely interconnected with homologous areas of the opposite hemisphere via commissural tracts, promoting interconnectivity between the two hemispheres.[60]

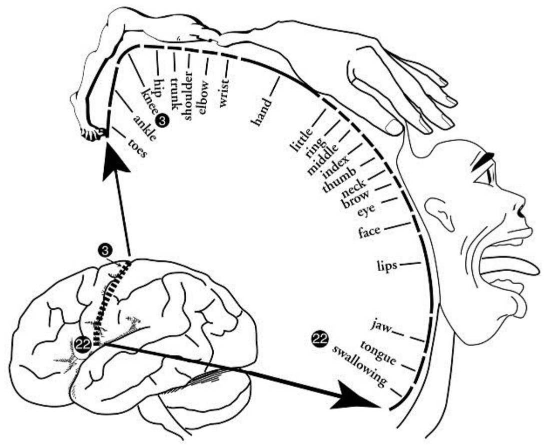

Figure 2.1: Homoculus

As suggested, the normally developing human brain is highly plastic and the motor cortex has the potential for rapid, large-scale functional change in response to motor skill learning.[61] Several studies of the sensorimotor cortex suggest that functional activity and corresponding cortex organization can be altered in humans by chronic experience. Cortex changes are observable following the acquisition of skill; examples of which include the representation of the skilled hand in the motor cortex map being expanded in string musicians[62] and blind Braille readers[63] as compared to the unskilled hand, and the representation of the digits in the motor cortex is reorganized in skilled badminton players.[64] Understanding the potential of plasticity in the normal, uninjured cortex provides a framework in which to explore plasticity in the injured or abnormally developed cortex in the hopes of improving physical function in patients with neurological impairment.

Neuroplasticity in Response to Injury

The developing (young) human brain can account for pre- and perinatally acquired lesions more effectively than the adult brain.[65] Lesions occurring prenatally (between 24 and 34 weeks gestation) typically compromise the competitive withdrawal process of the cortical-spinal tract,[66] thereby causing a unique re-wiring within the sensorimotor system. For example, in unilateral CP, the existing uncrossed projections from the non-lesioned hemisphere assume control of the affected hand and are strengthened during continued development and environmental interactions. Conversely, the weaker crossed (no longer dominant) projections from the lesioned hemisphere withdraw, at least partly.[66,67] The non-lesioned hemisphere, now controlling to some degree the movement of both the contralateral and ipsilateral hand, eventually becomes equipped with fast-conducting uncrossed projections to the affected upper limb.[48,68,69] To varying extents, cortical-spinal reorganization can occur throughout the pre- and perinatal period,[66] during the first month of life,[67] and in one case report, up to the age of two.[70] Many children 'relying' on ipsilateral projections show a useful grasp function with their paretic hand, some even with preserved individual finger movement,[71] while others cannot use their paretic hand for grasping, despite the presence of fast-conducting ipsilateral pathways indicating that ultimate function is at least partially dictated by different stages of development[65] and that lesions occurring earlier in development should result in better paretic hand function.[66] Conversely, no useful hand function is regularly observed with injuries occurring around birth or postnatally, despite the presence of ipsilateral tracts.[66,67] The functional relevance of ipsilateral control of the affected hand remains ambiguous as there are currently no known associations between lateralization and function.[60]

Unilateral brain damage that occurs during the period of cortical-spinal tract refinement also has a particular signature wherein the development of the non-involved hemisphere is also affected.[72] In the development of a kitten model mimicking unilateral CP, neurons within the developing M1 were silenced pharmacologically during weeks 5 and 7 of postnatal development[50] resulting in the formation of bilateral cortical-spinal tract projections from the non-involved hemisphere and sparse contra-lateral connections from the impaired hemisphere. In addition, the spared cortical-spinal tract projections underwent a structural plasticity so that terminations were now made in aberrant regions of the dorsal spinal cord grey matter, rather than in the ventral regions.[73,74] Animals in the study, despite no presence of lesion, displayed permanent motor impairments, including: overstepping and clumsiness during visually guided walking on a horizontal ladder, aiming errors during reaching, and grasping errors.[75,76] Considering the motor dysfunction within the cortical-spinal tract from the basis of a neural-circuit framework, two highly relevant changes are the loss of contralateral cortical-spinal tract connections from the damaged cortex and the maintenance of aberrant ipsilateral cortical-spinal tract connections from the non-involved cortex.[72]

While the loss of contralateral cortical-spinal tract connections is a key driver in impairment following unilateral brain injury, re-establishing these connections is necessary, but not sufficient, for motor recovery. The timing of training applied to promote the re-establishment of neural connections is also important. A study by Friel and colleagues in 2012 replicating unilateral CP in a group of kittens examined the effects of restraint and reaching training applied immediately after establishing an aberrant cortical-spinal tract and when applied after waiting until feline adolescence (20 weeks). Even though all groups demonstrated cortical-spinal tract restoration, only the early training group showed motor recovery, with neither the delayed group, nor the control group receiving no targeted training, displaying behavioral improvement.[7] The results of this study demonstrate that cortical change does not uniformly translate to functional improvements. Interventions must be sought that reach a threshold that promotes neuroplastic changes within the brain that translate to functional behavioral improvements.

'Vicarioation of Function' is a term that suggests that cortical or subcortical structures that are either adjacent to or remote from a damaged area of the brain can "take over" the function of the compromised areas.[77] There is significant evidence that motor recovery after cortical injury occurs in large part through behavioral compensation, rather than via a true recovery or restitution of normal motor strategies[78,79]. These compensations will be discussed later relative to rehabilitation; however, over the past two decades, substantial evidence has been produced to suggest that the adult cerebral cortex is capable of significant functional plasticity. Furthermore, results from both human and animal studies are converging to suggest that post injury behavioral experience, potentially rehabilitation, is a primary modulator of both the neurophysiologic and neuroanatomic changes that occur.[80] If changes in synaptic strength in horizontal connections and synaptogenesis can underlie functional modifications in the motor cortex of normal animals undergoing motor skill learning, it follows that these same mechanisms may play a role in recovery after damage to the motor cortex.[81]

Although we know that findings from animal models do not translate specifically to recommendations for human performance[4], evidence can be used to deduce and guide future treatment.

Because of the dynamic capacity of the sensorimotor cortex, demonstrated through numerous studies[82-86] following behavioral training, it is expected to undergo significant changes in functional organization following cortical injury.[80] Additional effects remote from the site of injury are also expected given that neurons in any damaged region of cortex have reciprocal connections with neurons in other regions.[60,80] Representational maps in the motor cortex can be altered by a variety of inputs, including changes in afferent sensory inputs, repetitive cortical stimulation, and pharmacologic interventions.[54,87] Prolonged alteration of tactile and proprioceptive inputs has been shown to produce plastic changes in the motor maps of rats. For example, in 1988, Donoghue and colleagues found that when the forelimb of either a perinatal or adult rat is amputated, the shoulder representation expands into former forelimb territory.[88,89] Reorganization of motor maps in M1 can also be produced by specific changes in motor behavior. Interhemispheric differences in the size and complexity of the hand representation in a monkey M1 has been correlated with laterality of handedness, suggesting that behavior can affect the organization of cortical representation.[10] Additionally, movement training programs in which monkeys were trained to retrieve food pellets from a small well[90,91] or rats trained to retrieve food pellets from a rotating disc[92] both results in a reorganization of movement representations on the motor cortex. After motor skill learning in normal animals, the motor cortex topography is reorganized and movements that are used in the newly learned task are represented over larger cortical areas.[90,92-94]

Neuroplasticity in Rehabilitation

While there is no singular, universally accepted definition, it is agreed that neuroplasticity is any change in neuron structure or function that is observed either directly from measures of individual neurons, or inferred from measures taken across populations of neurons.[3] From a rehabilitation perspective, this definition does not account for changes in behavior. In that, changes in motor output do not necessarily equate to neuroplastic changes occurring in the brain, nor does measured neuroplastic changes correlate directly with improved functional movement patterns. It is therefore critical that we acknowledge both sets of information to assess how neuroplasticity is supporting improvement of function during rehabilitation activities.[3]

Following neurological injuries, one of the most common behavioral consequences is that individuals develop compensatory behavioral strategies.[95-97] Animal research has indicated that these compensatory behaviors can be key drivers of what is considered to be a normal response to brain damage,[98,99] as reliance on the less affected limb following unilateral cerebral damage has been associated with major restructuring and neuronal growth in the uninjured hemisphere.[100-102] While such self-taught behaviors can be adaptive and become contributing factors to positive functional outcomes,[79] many can be maladaptive and interfere with improvements in function that could otherwise be obtained during rehabilitation. For example, after unilateral brain damage, reliance on the less affected side of the body is associated with significant neuroplastic change in the unaffected hemisphere that may produce immediate improvements in function. However, this reliance may also limit the propensity of individuals to practice behaviors that would improve function on the impaired side of the body.[103] In animal models, functional use of the distal extremities can be regained following an injury to the cortex. After large lesions to the sensorimotor cortex, however, motor tasks are more often performed using alternative motor patterns. For example, if left untrained, rats who have difficulty manipulating objects with their forepaws will use their mouths, rather than forepaws to collect food.[104] Following focal lesions in the primary somatosensory cortex area of the hand, monkeys gradually reacquire motor skill of the hand, accompanied by reemergence of representation within the cortex.[77] The details of the topographic reorganization depend on the type of post-lesion training experienced by the animal. In the absence of training, spared finger representation will undergo a further reduction in territorial representation. However, with daily repetitive training, spared finger representations are retained, suggesting a role of the adjacent undamaged cortex during recovery.[90,105,106]

These findings support previous studies agreeing that training is necessary. In separate works by Nudo and colleagues, in post-lesion monkeys who were allowed to recover spontaneously, the remaining, undamaged hand representation decreased in size.[86] Furthermore, at one month post-lesion, the total spared hand representation was reduced by over 50%. Over the ensuing months, a gradual recovery occurred, but full restoration of the motor map was rarely achieved.[82]

Previous work in animals has suggested that skill training, not merely repetitive use, is a key component in effective rehabilitative training. This finding has been consistent in both rats[107] and monkeys[82,91]. Indeed, multiple studies have corroborated this statement. A 1998 study by Friel and Nudo examined seven healthy adult squirrel monkeys.[108] Each monkey underwent training on a task requiring manual skill. Following task acquisition, a small lesion was made to the hand area of M1, sparing 62-74% of hand representation. Following surgical recovery, each monkey received daily rehabilitative training. After training, pre-infarct movement patterns returned in some animals, with others engaging in alternative movement patterns. Following one month of training, motor efficiency had recovered to near baseline for all animals, but kinematic analysis revealed significant changes in movement strategy.[92] In a complementary follow-up study, post-infarct monkeys were divided into two groups and participated in rehabilitative reaching practice from large or small wells. Those monkeys practicing retrievals from a large well displayed accurate performance from the beginning of training. Monkeys trained with the small wells, requiring skilled use of the digits, demonstrated progressive incremental performance over 10 days. No task-related changes in the cortical motor map for hand representation were observed for the large well group, whereas the small well group demonstrated movement specific changes that were large and consistent.[91] These findings offer further proof that skilled motor acquisition, or motor learning, is a prerequisite factor in driving representational plasticity in the motor cortex.[91]

With the understanding that the structure and function of the cerebral cortex are malleable following injury, treatments that attempt to maximize neuroplasticity are becoming increasingly popular. In parallel with the behavioral interventions in multiple animal studies, several human studies have demonstrated that intensive practice can result in further recovery in adult stroke patients.[109] One such approach is to apply robotic technology to support neuroplastic rehabilitation.

Robotic-Assisted Rehabilitation

Robotic-Assisted Rehabilitation remains a relatively novel and emerging rehabilitation option. A robot is capable of controlling and quantifying the intensity of training and objectively measuring changes in movement kinematics and forces; and, is defined as the application of electronic, computerized control systems to mechanical devices designed to perform human functions.[15] Besides providing new options for treatment, this technology may further our understanding of the mechanisms that underlie the recovery of motor function after stroke, such as the motor learning process and neural plasticity.[21,31] Research regarding robotic-assisted rehabilitation first began to proliferate in the mid 1990's,[45] and has continued to become more robust[15]. The sustained growth of interest in therapeutic robotics in recent years is due to a significant shift away from assistive technology for people with disabilities toward robotic therapies, which use the technology to support and enhance clinicians' productivity and effectiveness as they try to facilitate the individual's recovery.[45] Robots are an attractive option for rehabilitation, and thus, a fertile ground for research because of the machine's ability to perform repetitive tasks in a highly consistent and controllable manner,[12,13] the fact that they do not experience fatigue,[110] as well as their reliability and applicability across a wide range of motor impairment.[111] Existing research indicates that robotic devices have a good potential to provide adjunctive therapy that can complement more functionally based, therapist-generated interventions. In addition to providing new treatment options, this technology may further our understanding of the mechanisms that underlie motor recovery and neural reorganization after stroke.[11,111]

Robots designated for rehabilitation can be divided into two categories: robots designed as compensatory tools to assist in performing lost skills such as manipulation or mobility[112,113] and those that have been developed from a training perspective, to remediate or retrain lost motor function following a disabling injury or disease. For the purposes of this review, only those robots in the latter category- those providing remediation and rehabilitation to assist patients in improving motor function- will be considered. Robots used for remediation purposes can provide intensive, reproducible, and task-specific movement therapy during planar, spatial, or bilateral training activities. Robots are able to address a wide range of treatment needs through active, active-assistive, or strengthening exercises and have been used to effectively treat patients with moderate to severe motor impairments.[21,22,24,114-116]

Unlike traditional therapy, robotic-assisted rehabilitation delivers training at a much higher dosage (i.e. number of practice movements) and/or intensity (i.e. number of movements per unit of time), resulting in hundreds, if not thousands, of repetitions in a single session.[107,117] Rehabilitation robots also continuously monitor and record patients' movement kinematics and dynamic responses to therapy. This feedback is not only used to quantify therapy outcomes, but also to design a robotic control loop that can tailor the therapeutic action of the robot to the patient's motor abilities.[12,13]

Robotic-Assisted Rehabilitation Design Features

In a 2007 review, Reiner examined technical differences between several robotic devices.[118] Robotic devices take the form of either an actuated robotic arm (i.e. a manipulandum) or end-effector design, or an actuated robotic suit that fits to the affected limb as an exoskeletal frame. The robotic devices have sensors that record movement data such as position, velocity and joint torques. Additionally, rehabilitation robots have actuators that enable them to move the subject's limb. Robots allow for more precise measurement, in terms of both kinematics and dynamics, of both initial impairment and impairment changes in response to treatment. Robots can be programmed to simulate a variety of tasks affording both high intensity and repeatability, similar to stereotypical patterns employed during therapy.[119,120] Robotic devices may also be used to apply novel forms of mechanical manipulation that therapists cannot replicate[121] and adapt to patients' performance, assisting them as needed during a given motor task.[12,122,123]

One such robot (and the focus of this doctoral project) is the MIT-MANUS Shoulder-Elbow Robot (Figure 2.2), whose development began in late 1989 as a robot for planar shoulder-and-elbow therapy.[124] The MIT-MANUS was designed for clinical neurological applications. Unlike many industrial robots, MIT-MANUS was configured for safe, stable, and highly compliant operation in close physical contact with humans. It's computer-control system modulates the way the robot reacts to mechanical perturbation from a patient or clinician, resulting in a compliant and gentle behavior.[45] The MIT-MANUS assists rehabilitation through a graded training sequence of planar

Figure 2.2 MIT-Manus Shoulder-Elbow Robot

reaching movements that patients perform through an end-effector arm of the robot. Targets, placed spatially in a clock-like pattern on a monitor in front of the patient[40], dictate reaching motions in sequential or random patterns (Figure 2.3).

Figure 2.3: Target presentation on MIT-Manus Robot

The therapeutic benefit of the MIT-MANUS is derived from the robots capability to “assist as needed”. The ability of the robot to assist, allowed by impedance control, produces a controlled, repeatable stimulation of the upper limb by passively moving the limb along a target trajectory[125] or by providing targeted forces to the arm that result in a desired movement or after affect.[126] The strength of robots such as the MIT-MANUS and others with low mechanical impedance, inertia and friction is that they are extremely compliant to a person’s attempts to move during training.[115,124,127] The impedance controller modulates how the robot reacts to mechanical perturbation from a patient making it extremely robust to the uncertainties of physical contact.[128,129] Sensors in low-impedance robots permit accurate and continuous measurement of key variables used to describe motor behavior; namely position, velocity and force. These measures provide valuable information about changes in motor capacities that underlie functional motor performance. This is in contrast to industrial robots that have been reconfigured for rehabilitation (e.g. mirror image movement enabler (MIME)) that are intrinsically position-controlled machines that do not yield easily to external forces such as human movement. Although position-controlled machines have therapeutic benefit,[116,125] they are not as sensitive in recording and responding to motor performance during a patient's attempt to create movement without robotic assistance.[127]

As impedance appears to be a crucial component in the development of rehabilitation robotics, Huang and Krakauer[111] attempted to define it conceptually through a visual representation of a ball-bearing: "Imagine a ball-bearing representing hand position at the bottom of a symmetrical concave well. The slope of the well wall provides the impedance that keeps the bearing at the center of the well. If the slope becomes steeper (i.e. higher stiffness) in one direction, [+ x], and flat (i.e. zero stiffness) in the opposite direction, [- x], the bearing will move toward the [-x] position. The shapes of the well can be modified such that the bearing encounters a low level of impedance in the direction of the desired trajectory and a high level of impedance in any other direction."[111]

Robotic-Assisted Treatment

The available literature on robotic studies demonstrates clear incremental reductions of motor impairment that offer the opportunity to improve motor performance.[15,130,131] To date, studies investigating the effect of robotic-rehabilitation in the adult post-stroke population far outnumber the studies investigating pediatric applications. However, the success of adult studies of robot-assisted therapy suggests that this approach may be well suited to the needs of children with moderate to severe hemiplegia.[44] Initial studies with children presenting with CP or acquired brain injury[28,40,42,45] have shown that robot-assisted therapy is well tolerated and potentially beneficial for the pediatric population. Because of the limitations in available literature of robotic-assisted rehabilitation in the pediatric CP population, it is beneficial to explore the evidence that exists within adult populations as well.[15,24,114,132]

Neuroplasticity and Robotic Rehabilitation

The human brain is capable of self-organization, or neuroplasticity,[133,134] so that training and rehabilitation offer an opportunity for motor recovery.[114,124] The scientific rationale for rehabilitation robots for the upper extremity is based on the concept of motor plasticity and on evidence that intensive repetition of movement promotes motor recovery following a stroke.[91,135,136] Neuroplasticity has been discussed previously in regards to physiological changes within the human and animal nervous system. The application of neuroplasticity within rehabilitation can be considered motor learning, as motor outcomes are the end-goal of therapeutic regimens and represent, at least theoretically, the manifestation of organic structural changes occurring within the brain.

Motor control scientists define motor learning loosely, considering it a fuzzy term that encompasses motor adaption, skill acquisition, and decision making.[38] Neurorehabilitation is based on two basic assumptions: that motor learning principles apply to motor recovery and that patients can learn. Robots, incidentally, provide the means to quantitatively test these two assumptions.[111] Motor learning and motor adaptation are two of the potential models for recovery that researchers are beginning to encode in the design of robotic treatments. While there is considerable debate on the differences between motor learning and motor adaptation, it is increasingly clear that motor adaptation and learning are two different processes.[111] It is generally accepted that motor learning allows limited generalization to occur while motor adaptation does not. For example, we define the initial acquisition of the ability to ride a bicycle (which can generalize and facilitate learning to ride a motorcycle) as motor learning but define the initial improvement in performance observed after several decades without riding a bicycle as adaptation.[18] Functional gains obtained via motor learning are maintained over time, while the results from motor adaptation are short lived.[111]

As stated earlier, motor cortex reorganization and behavioral changes are not mutually inclusive constructs. However, principles that are consistent with producing measured cortical change in animals can be applied to treatment techniques in humans. These principles follow the basic model of motor learning. In 2008, Kleim and Jones produced an article outlining motor learning principles that are consistent with knowledge gained from animal models and that can be applied in clinical settings.[4] Those principles will be summarized here:

Use it or lose it: Neural circuitry that is not actively engaged in task performance for an extended period of time begins to degrade. Failing to engage a brain system due to lack of use may lead to further degradation.[137] This can be manifested in stroke survivors through learned dis-use of a paretic extremity, but can be prevented or rehabilitated through the promotion of functional reorganization during rehabilitation of a skilled task.[106,138] Combining rehabilitative training with constraint of the ipsilesional arm in humans with unilateral strokes improves the function of the impaired limb and promotes greater movement-associated activation in the remaining cortex of the injured hemisphere.[139]

Use it and improve it: Plasticity can be induced within specific brain regions through extended training. Monkeys trained to perform fine digit movements by retrieving small food pellets our of a well had an increase in digit representation areas within the primary motor cortex,[90] whereas rats trained to reach outside of their cage to retrieve food had an increase in distal forepaw representation within the motor cortex.[92]

Specificity: Skill acquisition is associated with changes in activation patterns in the motor cortex[94,140] and in movement representations.[93,141] In rats with unilateral cortical infarcts, several weeks of motor rehabilitation in skilled reaching with the impaired forelimb improved function and resulted in a major increase in the cortical territory associated with the reaching activity. However, performance of unskilled movements was not sufficient to reproduce the effects of skilled reach training on motor maps.[107,142] Learning-induced brain changes show regional specificity. Unilateral training in reach and grasp tasks in rats causes dendritic growth in the motor cortex contralateral to the trained limb, but only subtly effects on the ipsilateral motor cortex.[143,144] Specific forms of neural plasticity and behavioral changes are dependent on the types of stimuli presented to the learner. Training in a specific modality may change a limited subset of the neural circuitry involved in more general function, and influence the capacity to acquire behaviors in non-trained modalities (i.e. patients may not be able to generalize practice that is non-specific).[4] Research in conventional stroke rehabilitation indicates that task specificity is a key factor in enabling efficacious recovery.[32] Task-specific and goal-oriented repetitive approaches, such as constraint-induced movement therapy[109,145] and treadmill training with partial body-weight support[146,147] have proven effective.

Repetition Matters: Some forms of plasticity require not only the acquisition of a skill, but also the continued performance of that skill over time. It is hypothesized that the plasticity brought about through repetition represents the representation of skill within the neural circuitry, making the acquired skill less likely to diminish.[148] Repetition in creating plasticity and learning may be critical for rehabilitation. A sufficient level of rehabilitation is likely to be required to see initial functional gains. Further repetition may then be necessary to obtain a level of brain reorganization sufficient for the patient to continue to use the affected function outside of therapy, and to even make further functional gains.[4]

Intensity Matters: "Practice makes perfect" is a common cliché that summarizes one of the fundamental principles of motor learning. Better performance is correlated with the time and amount of practice devoted to learning a particular skill.[149] It has been noted that there is a dose-dependent relationship between acute and sub-acute post-stroke therapy and outcome.[135] Dosage has been found to be an important component within rehabilitation suggesting that 400 repetitions is a critical level- where at animal data shows changes in synapse density in the primary motor cortex.[107,117] Alternatively, low-intensity stimulation can induce a weakening of synaptic responses, also known as long-term depression, rather than inducing long-term potentiation as occurs with high intensity stimulation.[150]

Studies on the dose-response relationship in stroke rehabilitation have shown that more intensive therapy is associated with an enhanced rate of motor recovery; and, no ceiling effect for intensity of therapy has been observed.[14,39] To improve arm and gait ability after a brain injury, an early and intensive therapy approach is advocated. The intensity of arm and leg therapy is positively correlated with the motor outcomes after stroke.[151] Despite these findings, traditional therapies are not typically delivered intensively or frequently, often because of the cost and labor limitations.[152]

Time Matters: If therapy promotes neural restructuring, then it should work anytime; but there may be windows in which it is particularly effective.[153] Time may be particularly critical following brain damage given the dynamic changes in the neural environment that occurring independent of any rehabilitation. A consideration in the timing of behavioral treatments may be whether treatment is primarily neuroprotective in nature- that is, sparing of neuron death and loss of neural connections, or whether the treatment works primarily by driving reorganization of the remaining connections, as typically proposed for rehabilitative training.[4] For example, training delayed until 1 month after the injury was effective in producing other changes in movement representations and in improving function, but it failed to prevent the loss of movement representation in peri-infarct cortex that was found in monkeys receiving earlier training.[154] Additionally, time delays also allow for the greater establishment of self-taught compensatory behaviors, some of which may interfere with rehabilitative training efforts.[4]

The importance of timing in neuro-recovery demonstrated in animal models is consistent with research in adult stroke rehabilitation. Studies have shown that the greatest gain in motor recovery occurs in the first month after stroke.[155-157] Encouragingly though, recent studies have demonstrated that gains in upper extremity function can occur in persons with impairments from chronic stroke, 6 months or longer from the initial injury.[21,22,24,116]

Salience Matters: In order for an organism to effectively function, there must be a system in place to weigh the importance of any given experience, so that it can be encoded effecitively.[4] Research using auditory tones as classical conditioning stimuli has provided evidence for such a system and demonstrated that plasticity within the auditory cortex is dependent upon the salience of the experience. Animals trained to recognize a tone of a specific frequency receive a reward, thus one tone becomes more salient than others and leads to an increase in the representation of the salient tone within the auditory cortex.[158] In motor rehabilitation, sufficient motivation and attention are essential to promoting engagement in the task (i.e. rats participating in rehabilitative reaching when it earns them a reward), as rewarding training has been found to improve motor function.[159]

Interference: Neural plasticity generally has a positive connotation when considered in the context of motor recovery; however, plasticity can also serve to impede behavioral changes. Interference refers to the propensity of plasticity to impede the consolidation of new, or expression of existing, plasticity within the same given neural circuitry. Patients recovering from neural injury may develop compensation strategies that are easier to perform (i.e. bad habits) than more difficult, but ultimately more effective, strategies promoted through rehabilitation. These strategies might be adopted earlier in recovery, and therefore used with much greater frequency than those targeted during therapy. Over-reliance on less-affected modalities may also exaggerate impairments as a therapy that benefits one skill may interfere with another.[4] Early skill training that was focused on the ipsilesional limb of rats with unilateral infarcts was found to worsen subsequent performance and decreased use of the impaired forelimb[160], suggesting that it contributed to learned nonuse.[161,162] When maladaptive, these self-taught compensatory strategies may induce plasticity that will have to be overcome with subsequent rehabilitation and other treatment approaches.[109,163,164]

Many clinical interventions are able to adequately address one, or even several, of these motor learning principles. Few, if any, clinical interventions are able to address all in such a way as to truly maximize motor learning. For clinical interventions to be maximally effective in the neurological arena, more effort towards incorporating all of the aforementioned principles must be realized.

Stroke

Stroke is a leading cause of long-term disability in the United States, affecting an estimated 6.4 million Americans.[165] Long-term disability is often associated with persistent impairment of an upper limb,[166] with hemiparesis, a blanket term that encompasses general weakness, motor control abnormalities, and spasticity, common.[111] The traditional goal of rehabilitation is to promote functional adaptation[114] and recovery relies on physical therapy practice philosophies that aim to restore neurologic control, rather than to merely use compensatory strategies.[167-169] However, motor outcomes following conventional rehabilitation of stroke are poor, only 30-66% of patients receiving conventional treatment are able to regain functional use of their paretic arm.[170,171] Additionally, ongoing cost containment measures and shorter rehabilitation hospitalizations have shifted therapy efforts away from attempts to restore lost motor abilities in the paretic limb and toward the teaching of compensatory techniques to improve functional skills. This change in rehabilitation services has occurred at the expense of impairment reduction.[172] Taub suggested that an emphasis on compensation early after stroke could lead to a pattern of learned nonuse and lower the potential for subsequent gains in motor function of the paretic arm.[147] Although studies have shown that the greatest gains in motor recovery occur in the first month after stroke,[155-157] recent studies have demonstrated that gains in upper extremity function can occur in persons with impairments from chronic stroke (longer than 6 months).[21,22,24,116] Furthermore, while the initial degree of stroke and paresis severity is a good predictor of upper extremity functional recovery,[157,173,174] task-specific, high-intensity exercises in an active, functional, and highly repetitive manner over a large number of trials have been shown to enhance motor recovery, even in chronic stages of stroke.[21] With the national medical model shifting away from acute treatment and skewing towards out-patient, ambulatory care, improved and efficient methods of rehabilitation will be necessary.

Robotic-Assisted Rehabilitation in the Adult Stroke Population

Robotic-assisted rehabilitation is effective in reducing upper extremity motor impairment when provided early following stroke[15,114,130,172,175-177] and also when applied during chronic stages of stroke recovery.[21,22,24,116] While some studies have demonstrated outcomes similar to those seen in conventional therapy approaches,[178-180] robots offer an ability to deliver repetitive movements at higher rates than that of conventional therapy. The number of movements generated in robot-assisted therapy is far higher than in other forms of therapy, such as electrical stimulation,[181] free-reaching,[182] and neurodevelopmental therapy.[116,125]

Studies with the MIT-MANUS robot have shown that intensive practice of upper limb movements contribute to statistically significant motor recovery after stroke. In a retrospective study of 56 patients who began rehabilitation less than 2 weeks after stroke, it was found that individuals who received conventional therapy plus intensive robotic therapy, 5 hours per week for 6 weeks, demonstrated statistically significant gains in upper limb motor abilities during both the first and last 3 weeks of robotic intervention. In contrast, patients whose primary treatment consisted primarily of conventional therapeutic techniques, had little to no change in motor function during this timeframe.[19] Although it is possible that features of robotic therapy other than intensity may have contributed to the observed gains in motor performance, it is clear that robotic training after the first 3 weeks elicited motor recovery that was not realized through conventional training alone.

Research has indicated that high intensity repetitive movements constitute an important contributor to the effectiveness of robot-assisted therapy. Researchers have attempted to match the intensity of robotic therapy to the number of movements generated by other forms of therapy[182,183]. These studies, designed to limit the amount of repetition provided by the robot, failed to show a differential effect between robotic and conventional treatment techniques. In other words, robotic therapy did not hinder or halt recovery, but had no particular advantage over conventional therapy at low levels of utilization. It is important to understand that robotic-assisted rehabilitation simply uses robots as modalities to deliver highly repetitive therapy. There is no reason to assume that robots will lead to better results than conventional therapeutic approaches if all other variables are constant.[15] The benefit of robotic therapy comes from the ability to deliver, through automated administration, therapy at dosages higher than is possible with conventional therapy.[111,183] How does high dose delivery potential impact the clinical decision-making of the therapist given the potential of robotics to delivery higher doses in shorter timeframes with potentially greater intensity? Can this be applied in chronic recovery situations?

To further investigate the effectiveness of robotic-assisted rehabilitation in reducing chronic motor impairments, research has been performed in the population of stroke survivors who are more than 6 months post stroke onset. These studies have the potential to further examine the process of stroke recovery and to investigate whether robotic therapy is effective after spontaneous neural recovery is thought to have ended. In one study, forty-two subjects, 1-5 years post stroke were treated with the MIT-MANUS 3 times per week, for 6 weeks. Statistically significant gains were found at discharge as measured by the Fugl-Meyer Assessment, Motor Status Score for shoulder and elbow, and the MRC Motor Power test.[21] These scores continued to be significantly better at the 4-month follow-up assessment.[20] In a separate study, significant benefits were also found in 30 subjects with moderate to severe impairments more than 6 months post-stroke who received robotic-assisted rehabilitation via the MIT-MANUS 3 times per week 6 weeks.[24] The results from these studies, indicating that a reduction on chronic motor impairment could be induced after a period of relative stability in function, suggest that there may be opportunities within the chronic stage of recovery for improvement, providing support that the receptivity to therapeutic interventions extends beyond the first 6 to 12 months; and that robotic-assisted rehabilitation is a modality capable of eliciting positive changes in motor abilities.[11]

One of the largest upper extremity, robotic rehabilitation studies to date was published in 2010 by Lo, Guarino, Richards, et al.[179] Lo and colleagues recruited subjects from VA medical centers who were 18 years old and older and had long-term, moderate to severe motor impairments of an upper limb resulting from a stroke at least 6 months prior to study inclusion. Subjects were randomly assigned to one of three groups: 1) robot-assisted therapy, 2) intensive comparison therapy, or 3) usual care. Robot-assisted therapy was administered a maximum of 36 sessions over a period of 12-14 weeks and was divided into four 3-week modules consisting of varying robotic interventions. The intensive comparison therapy consisted of a structured protocol using conventional rehabilitative techniques, such as assisted stretching, shoulder-stabilization activities, arm exercises, and functional reaching tasks. The intensive therapy protocol was designed to match the robotic-therapy group in both schedule and in the intensity of movements.[180,184] The usual-care group received customary care that was available to all patients (i.e. medical management, clinic visits as needed, and rehabilitation services) which was not dictated by the protocol.

Evaluations were performed at 6, 12, 24, and 36 weeks following randomization with the primary outcome measure being the Fugl-Meyer Assessment. Long-term, at 36 weeks, patients receiving robot-assisted therapy had significant improvement in Fugl-Meyer scores as compared to those receiving usual care, with no significant difference between robotic-assisted therapy and intensive comparison therapy observed.

The improvement observed in the two active-therapy groups during the 36 week study period suggest that high-intensity, task-oriented movement training may be necessary for motor recovery. It is not known whether a shorter duration of therapy or fewer movements per session could have a similar effect because the robot-assisted training was delivered in a progression of four modules over the 12-week treatment period. The study provided evidence of the potential long-term benefits of intensive rehabilitation in patients with moderate-to-severe impairments years after stroke, but did not differentiate robotic-assisted training in this particular training protocol when looking at clinical outcome measures.

Robotic rehabilitation studies have generally reported beneficial effects on impairment measures but have not proved effective with respect to functional outcomes. In a systematic review of eight robotic-assisted trials, Prange and colleagues concluded that robotic therapies led to a long term improvement in motor control by increasing speed, muscle activation patterns, and movement selection, although no consistent benefit was found with ADL measures.[130] In a separate review, Kwakkel and colleagues also concluded that ADL's did not significantly improve despite obvious improvements in impairment.[15] One reason for these outcome measure-dependent results may be that common functional assessment scales are insensitive to improved performance at the level of impairment in the affected limb, focusing instead on the level of compensation. Conversely, increases in movement range and force may have real-life implications despite not translating to improvements in ADLs.[180,185]

Indeed, most robotic-assisted rehabilitation studies have relied primarily on traditional clinical measures of motor impairment as their primary outcome.[20,21,24,116,186,187] Only a few studies have reported on the robot-derived outcomes inherent to machines such as the MIT- MANUS.[17,30,188,189] The robot-generated measures inherent to the MIT-MANUS in particular have demonstrated the ability to detect significant improvements in motor performance, even when the associated clinical measures in the study revealed only small changes.[188,189] The sensitivity of these measures allows researchers to look beyond clinical measures, and to quantitatively explore aspects of recovery that have traditionally relied on qualitative observation, such as smoothness of movement,[189] muscle tone,[190] and synergies.[17]

A 2015 study by Massie and colleagues[30] explored the used of robotic measures to better explain subjects' responses to robotic-assisted therapy. The purpose of the study was to investigate how kinematic data, specifically movement time (the amount of time that it took participants to move between the central target and one of the eight peripheral targets on the MIT-Manus robot), could characterize motor performance changes following MIT-MANUS robotic intervention. A secondary aim of the study by Massie et al. was to assess whether a within-session regimen of 45 minutes of repetitive reaching training, followed by 15 minutes of transition to task practice would produce the same timeline of kinematic changes as a treatment intervention of 60 minutes of robotic-training only. Participants in the study were 22 subjects with chronic stroke impairments. All participants had a Fugl-Meyer intake score of 7 to 38 and possessed adequate arm mobility to move the robotic manipulandum to target locations.

Within the study, participants completed 3 days of therapy for 4 weeks. Each session consisted of 60 minutes of therapy, with one group receiving robotic-training only and the other group receiving 45 minutes of robotic training paired with 15 minutes of transition to task practice. From the study, improvements in movement times were similar after 12 sessions for both groups; however, in an expanded analysis, it was determined that the gains in each group were achieved differently. The robotic-training/transition to task practice group had a greater rate of improvement during the session which was not maintained between sessions, whereas the robotic-training only group had smaller gains within a session, but also demonstrated a small gain between sessions. The properties of the robot allowing for the collection and reporting of finite data below the threshold of traditional clinical measures allowed for the observation of differences in response to training that would have otherwise been undiscovered.

Cerebral Palsy

The term "cerebral palsy" describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.[26,27,191] CP is the leading cause of childhood disability, with an incidence of 2-3 per 1000 infants diagnosed each year,[192] and has a profound effect upon physical function.[193] CP is a disabling syndrome challenged by a broad spectrum of clinical symptoms. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems.[27] Upper extremity dysfunction commonly occurs in CP and can negatively affect a child's ability to perform activities of daily living, as well as limit their participation in family, school and leisure activities[194] because of potential developmental disregard to the paretic limb.[192]

Depending upon the location of the lesion within the brain, CP can result in varying presentations.[195] Hemiplegia occurs in approximately one-third of diagnosed cases of CP,[196] is the most common syndrome in children born at term and is second in frequency only to spastic diplegia among preterm infants.[197] The etiology of hemiplegia in children can be attributed to perinatal stroke that occurs between 28 weeks gestation and one month of age, or to forms of acquired brain injury such as childhood stroke.[198] Stroke in young children often results in cognitive and movement disorders that are very similar to those seen with hemiplegic CP.[199] Therefore, patients diagnosed with stroke, or "acquired brain injury" occurring up to 2 (or 3) years of age are typically grouped with patients having a classical CP diagnosis.

The goal of rehabilitation in children with CP, or hemiparesis, is to improve independence in daily life activities, reduce the burden of care for the family, as well as to improve the quality of life for both the young patient and his or her family.[200] Typical rehabilitation for children with hemiplegic CP uses purposeful activity and task-specific training to improve motor function and independence.[201,202] Motor learning strategies that incorporate practice, repetition, and functional context are commonly used in occupational and physical therapy practice[43] and are considered essential to successful therapy for pediatric movement disorders.[203,204]

Current motor learning theory describes a correlation between improved motor function and the use of massed or repetitive function,[81] but massed practice is difficult to achieve during typical pediatric therapy sessions. The success of the rehabilitation process depends on several factors: the intensity of the therapy, repetition, and a goal-oriented and task-specific training program are considered essential in achieving a favorable outcome.[135,205,206] However, rehabilitation programs tailored to the special needs of an individual child are personnel intensive and, therefore, expensive. Often, limited resources decrease the success of rehabilitation due to sub-optimal therapy conditions and limited dosage of therapy treatment.[200]

Independent of the approaches used in the rehabilitation process, conventional interventions, or new rehabilitation technologies, children with CP would benefit from periods of intensive therapy interventions enhancing motor development.[207] The integration of more intense and task-related exercise strategies and the comprehensive combination of noninvasive treatment, surgical interventions, and new technologies has been initiated to improve rehabilitation strategies.[208] Much of the initial intervention work that incorporated research based on brain plasticity has been developed based on adult stroke literature, wherein multiple studies have demonstrated the efficacy of constraint-induced movement therapy, treadmill training, robotic training, neuromuscular stimulation and virtual environments.[209] These interventions are similar in that they are intensive, structured and task oriented; in addition to the fact that they are beyond the norm when describing current customary care. As such, it is notable how slowly these interventions are becoming accepted and implemented within the rehabilitation community. Schertz and Gordon[210] reflect in an opinion piece that the lack of awareness amongst the rehabilitation community of emerging technology and treatment techniques is likely mostly to blame for the slow adaptation of new interventions. As such, the authors do caution therapists to take notice, stating: "Provision of ongoing, once- or twice- weekly therapy that lacks functional goals and rigorous measures of change should be strongly questioned. Conversely, in a recent study, traditional and conductive education therapies for children with CP were provided with high intensity yet were not found to be efficacious.[211] Therefore, intensive application of a therapy that lacks a task-oriented approach should also be reconsidered. Thus, it appears that treatment intensity is necessary but not sufficient."

Robotic-Assisted Treatment in the Pediatric Cerebral Palsy Population

Effective interventions to improve upper extremity motor function in children with CP use repetitive practice of goal-directed tasks with sufficient visual and auditory feedback.[212,213] Recently, robotic therapy has been explored as a method for improving motor performance in children with CP.[29,44,45] Based on the evidence presented earlier supporting the use of therapeutic robot-assistive in the rehabilitation of impairment and disability following stoke,[15,24,114,179] researchers are exploring the use of these devices as a potential tool in the treatment of CP.

Several studies have suggested that motor recovery following stroke or motor habilitation in children with CP resembles some form of motor learning,[214] but the extent of this relationship is not well understood. There is strong evidence that the organization of the brain cortex is dynamic and that it is directly induced by the type and intensity of the activity and context. While this appears to be true in the adult brain, there might be an even bigger window of opportunity for plasticity during childhood.[215] There is growing consensus that training might have a positive impact on CP and other acquired brain injuries in children through the reprogramming of spared neural tissue, i.e. a reorganization of the remaining cortical subcortical networks and their descending projections,[216-219] perhaps even more so than adults.[29] Models representing stroke recovery start from the inherent principle that subjects had learned and perfected the neural network that drives and controls movements over the course of thousands of repetitions, through many variations of countless purposeful actions. Following a stroke, this network is disrupted and rehabilitation efforts aim to restore the effectiveness of partially disrupted pathways or strengthen complimentary neuromotor connections. Contrary to this, neural networks in the CP population are still immature at the time of the lesion. Rather than reestablishing disrupted pathways as in stroke, rehabilitation strategies aim to assist children as they mature and to teach them skills within the limits of the spared pathways, and, perhaps, also strengthen alternate neuromotor networks to maximize their full potential.[31]

Because of the nature of growth and development, most interventions for CP take place several years post-injury.[220] Pilot studies using robotic-assisted therapy in children[42,43,221] and one adult[45] with CP have shown that both pediatric and the adult patients can benefit years after their diagnosis. Rehabilitation robots can provide controlled and intensive task-specific training, a rehabilitation concept that is consistent with the stated emphases of appropriate therapeutic interventions for upper extremity training in children with CP.[44,45]

A study by Fasoli and colleagues in 2008[43] examined the use of the InMotion2 robot (a commercialized version of the MIT-MANUS) with children diagnosed with severe hemiplegia due to CP or acquired brain injury. Twelve children between the ages of 4 and 12 completed 16, one hour robotic sessions. Each participant performed 640 repetitive, goal-directed planar reaching movements with his or her paretic arm during each therapy session. If a child was unable to maintain active grasp of the robot handle, the least-restrictive assist (grasping mitt or foam strapping) was used. The authors reported that the robotic-therapy games were cognitively engaging, highly intensive, and functionally relevant in that they focused on improving transport of the limb and reaching abilities needed for everyday tasks. Additionally, the study protocol was similar in frequency and duration to those of conventional rehabilitation programs for children with hemiplegia.

Following robotic training, statistically significant improvements in upper limb coordination and quality of movement were found on the two primary outcome measures, the Quality of Upper Extremity Skills Test (QUEST) ($F = 8.41$, $p = 0.001$, $r = 0.49$) and the Fugl-Meyer Assessment (FMA) ($F = 38.01$, $p = <0.0005$, $r = 0.73$). The QUEST is an outcome measure that evaluates movement patterns and hand function in children with cerebral palsy[222], whereas the FMA is a stroke-specific, performance based impairment index designed to assess motor function, balance, sensation, and joint functioning in patients with post-stroke hemiplegia.[223] A review of individual scores revealed that the greatest improvement occurred in the shoulder and elbow items of the FMA and QUEST. Additionally, statistically significant improvements with small to moderate effect sizes were found for the Modified Ashworth Scale and isometric elbow strength. The results of the study suggested that robotic-training produced a significant improvement in arm coordination and quality of movement, with a less impactful improvement found in spasticity and strength.[43]

A similar study, by Frascarelli and colleagues[40] in 2009 also found positive results in children with CP participating in training with the InMotion2 robot. In Frascarelli's study, 12 children between the ages of 5 and 15 with moderate CP due to hemiplegia or acquired brain injury participated in robot-mediated therapy during a one hour session, three times per week, for six weeks. In this study, participants completed only 384 repetitions of goal-directed planar reaching movements with the paretic arm during therapy sessions. Despite the decreased amount of repetitions, participating children demonstrated significant improvement in the Fugl-Meyer Assessment ($t = 4.16$, $p = 0.002$, $r = 0.8$), Modified Ashworth Scales ($t = 4.21$, $p = 0.001$, $r = 0.3$), the Melbourne Assessment Scale ($t = 5.20$, $p = 0.002$, $r = 0.3$) and several intrinsic robotic assessments. Clinically, the authors reported that participating children were better able to move their paretic arm in reaching movements and to control the synergy and the coordination of shoulder, elbow, and wrist.[40]

The positive results of these two studies, suggests that robotic-assisted therapies possess benefits for children with hemiplegia at varying amounts of repetition. These results, positive outcomes associated with varying dosage levels, have been corroborated in adult stroke studies[224,225], suggesting that intensity (dosage) is indeed an important component of robotic rehabilitation.

Beyond repetition of training, robotics possess other intuitive features that may prove advantageous in the delivery of rehabilitation to the pediatric CP population. A 2014 systematic review conducted by Chen and Howard[226] suggested that possible mechanisms contributing to the success of robotic interventions in children include an encouraging and positive environment highlighted by positive feedback when practicing arm movement,[227-229] provision of visual and auditory feedback to promote motor learning,[213,230] and customization of provided forces via real-time impedance control.[42,43]

Additionally, robotic rehabilitation can be modified in such a way as to augment the delivery of training. A 2013 study by Landeheim and colleagues[29] examined the outcomes of robotic training when children were trained via a sequential presentation of targets versus those trained via a random presentation of targets. Based upon concepts of the contextual interference theory,[231] it would be predicted that the sequential treatment group would have better initial results and that the random treatment group would have longer lasting results. The Landeheim study evaluated this concept by randomly assigning 31 children (15 male, 16 female) with a diagnosis of hemiplegic CP to two groups. Each group participated in 960 repetitions of robotic-assisted training on the

MIT-MANUS robot; with group 1 receiving a sequential presentation of training targets and group two receiving a random presentation. While all groups demonstrated a significant improvement in clinical measures (Pediatric Evaluation of Disability Index, Modified-Ashworth Scale, and Fugl-Meyer Assessment) as a result of the robotic-training, there was no difference between the two groups.[29]

There are several factors that may limit the application of this theory to the current delivery of robotic-assisted training and may, therefore, affect the significance of the expected result. First, the tasks practiced within the robotic training may be rapidly learned so that differences may be limited to early trials. Secondly, although the targets appear in a different presentation (sequential v. blocked), the distance to the target and the return motion are identical. Over the course of a thousand trials, the different training paradigms may not have presented enough of a challenge, or variation, to the subject from a motor learning perspective.[29] Additionally, the outcome measures utilized in the study were not based on the tasks used during training. The random presentation findings in this study did complement earlier research[37,232] that has reported better translation of motor control to novel tasks, as compared to block practice. The inclusion of a functional outcome measure that assessed the application of learned movement within a novel task may have better represented changes in the random presentation group.[29]

Regardless of study outcome, the early literature within the pediatric population and the application of robotic-assisted rehabilitation can improve our understanding of motor skill acquisition and begin to model this process.[42,45,221] An inherent feature of robotics, which was discussed previously within adult stroke studies, is robot-based metrics that allow researchers to investigate whether the kinematics of unassisted movements can improve with training (acquisition of motor skills) and whether this improvement remains at follow-up (retention of motor skill gains). The use of robotic measures allows a level of sensitivity to change that is potentially missed within the examination of clinical measures applied in the traditional pre-, post- and follow-up method.

Fasoli and colleagues[44] explored the use of robotic metrics within a controlled study that consisted of 12 children, aged 5 to 12, with diagnoses of hemiplegic CP (and one child with traumatic brain injury). Participants performed a robotic protocol on the MIT-MANUS similar to previous studies: one hour robotic therapy sessions, 2 times per week for 8 weeks. As with previous studies, clinical scores showed a significant change from baseline to discharge in all utilized scales; including: Fugl-Meyer (18.92 to 26.92), QUEST (58.63 to 66.12), and the Modified Ashworth Scale (6.58 to 5.08). Additionally, the kinematic robotic-measures including movement duration, deviation from the straight line, and smoothness all showed statistically significant changes from baseline to discharge ($p < 0.05$), with the aim improving, the deviation from the straight line decreasing, and movement smoothness increasing. Hence, in this study, changes observed in the kinematic outcome measure occurred as children also improved on the utilized clinical measures.[44] In future studies, the sensitivity of inherent robotic-based kinematic measures may allow researchers to more precisely identify the rate of change during robotic interventions, whether those changes corroborate with associated clinical measures or not.

Summary

Research has shown that the human brain is capable of restructuring in the presence of appropriate stimuli. When faced with injury or impairment, this knowledge allows the rehabilitation community to refocus efforts, with an emphasis placed on regaining normal movements through the facilitation of restored neural pathways rather than developing strategies to compensate for lost function. This review has outlined the advances that have been made within robotic-assisted rehabilitation. Though it is still an emerging field, preliminary findings have supported the application of robotic-assisted interventions in the neurologically impaired adult and pediatric populations. In the clinical arena, progress has been made in producing functional change and cortical re-organization with constraint-induced therapy.[233,234] As robotics affords clinicians increased opportunity through its inherent treatment principles, and through its ability to capture real-time performance metrics, more research is needed to optimize the implementation of robotic-assisted interventions within rehabilitation, and to fully appreciate the opportunities it presents.

Chapter 3 : Methodology

Study Overview

This study was a randomized pre-test, post-test, and follow-up investigative study to determine if there was a difference in clinical outcomes of children with hemiplegic cerebral palsy (CP) participating in two different applications (blocked presentation or random presentation) of robotic-assisted upper extremity training. Previously reported are the changes in clinical measures[29] resulting from participation in this robotic rehabilitation protocol which will be detailed within this chapter. Secondary analysis of the data sought to evaluate performance trends within those participants to further examine dosing implications. This chapter details the subject population, protocol (Figure 3.1), and data collection of the study and also details the methodology used to analyze the kinematic data for the secondary analysis.

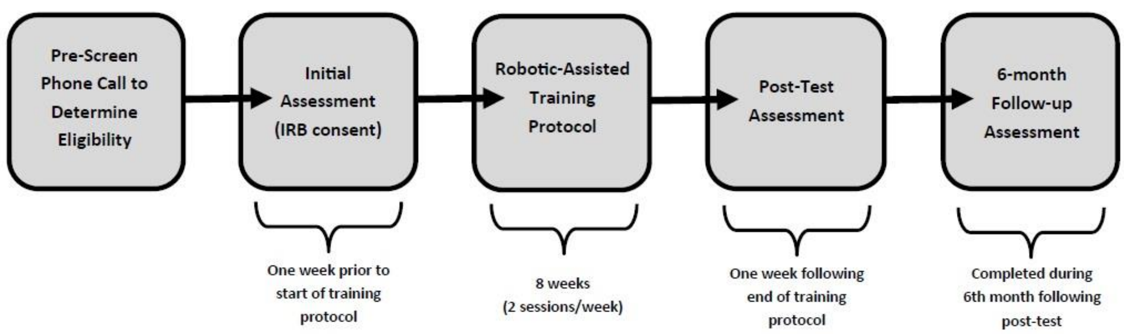

Figure 3.1: Study Timeline

Study Participants

Inclusion Criteria

Inclusion criteria for the study included: 1) children between the ages of 4 and 14, 2) a diagnosis of hemiplegia CP or ABI more than 6 months prior to study enrollment, 3) moderate or less than moderate spasticity in the affected upper limb, as demonstrated by a Modified Ashworth Score of 2 or less in the shoulder, elbow, and forearm and 3 or less in the wrist and fingers, and 4) adequate range of motion to engage in robotic therapy tasks, with passive range of motion in elbow extension of -25 degrees or better, and wrist extension greater than or equal to neutral.

The inclusion criteria were set to attempt to capture a subject population that was as homogeneous in injury as possible, as well as appropriate for upper-extremity robotic-rehabilitation on the MIT-Manus Shoulder-Elbow robot. The minimum age of 4 years old was established to attempt to ensure that children initially included in the study had a long enough reach to complete all portions of the robotic activities. Additionally, 4 years old was a minimum cut-off to allow all participants to be cognitively mature enough to participate in the intervention activity. The maximum age of 14 was set to maintain a population that was still developing cognitively and was in the purposed "sweet spot" of neuroplasticity as suggested in Kleim's earlier work.[4] The intention of this study was for all participants to have a diagnosis of hemiplegic CP. Acquired Brain Injury (ABI) was included as an acceptable diagnosis if the injury was sustained prior to 3 years of age as most definitions of CP include post-natal injuries up to 3 years after birth.[27] The criteria for minimum tone and range of motion requirements were established so that all children could complete the required robotic activities without limitations from musculoskeletal impairments.

Exclusion Criteria

Exclusion criteria for the study included: 1) having received botulinum toxin or phenol injections within 4 months of the start of the study or being scheduled for any type of surgical procedure over the course of the study, 2) upper extremity surgery less than 6 months prior to enrollment, 3) uncontrollable seizure disorder, and 4) insufficient ability to follow directions during a 60 minute evaluation or treatment session (including frequent breaks). Enrolled subjects who began participation in new therapy or research protocols during the course of the study were removed.

As with the inclusion criteria, the exclusion criteria was established to ensure that all children enrolled in the study could successfully attempt the intervention and also to reduce risk. Because botulinum toxin and phenol injections do not have a steady rate of effectiveness, that is, the responses to the medications have a half-life,[235] their presence could impact the response of children to training. Additionally, because of the recovery and potential improvement in function absent of robotic intervention following surgery, those children were excluded from the study. The robotic intervention protocol required that all children complete the entire training session each day, therefore any child who could not attain to a task for 60 minutes (with rest breaks allowed) was excluded as they would not have been able to finish the sessions. Last, while there has been no report of participation on the MIT-Manus robot causing seizures, the robot does present with bright and flashing targets. Therefore, out of caution to some of the known triggers of epilepsy, those with a history of uncontrolled seizures were also excluded.

Concurrent Therapies

All patients enrolled in the study were permitted to continue their current, community-based therapy regimen with certain caveats. If, through parent report, a child's occupational therapy protocol was focusing predominantly on upper extremity gross function rather than a focus on integration of ADL's, it was requested that the child cease occupational therapy during the intervention portion of the study, or to switch focus of training to ADL development. Additionally, per the exclusion criteria, children were requested to delay any scheduled botulinum toxin or phenol injections until conclusion of the study following the follow-up assessment.

Recruitment | Consent | Retention

Children were recruited for the study through the Cerebral Palsy Clinic at Riley Children's Hospital at Indiana University Health, the Pediatric Rehabilitation Department at Indiana University Health, and through word of mouth with pediatric therapists and parent groups within Central Indiana. Upon patient interest, a pre-screening evaluation [Appendix A] was conducted via phone to determine eligibility (minus clinical range of motion measures) of enrollment. Final eligibility for study inclusion was determined during an initial visit in which range of motion and tone screenings (Modified Ashworth) were performed.

Human Subjects Involvement and Characteristics

All recruitment procedures were reviewed and approved by the Indiana University Purdue University at Indianapolis Institutional Review Board (IRB), study number 0911-65 [Appendix B] prior to initiation of the study.

Benefits of research to human subjects and others

Participants were notified via the informed consent/assent process that no expectation regarding improvement of condition should be expected as a result of participating in this research project. Because the benefits of robotic therapy for children with CP have not been fully studied, this form of therapy may not be effective in children.

Participants were advised that potential benefits may occur following participating including improving functional use of the weaker arm and increasing ability to reach for or stabilize objects.

Study Design

Robotic device

Intervention was provided by the InMotion2 robot, the commercial version of the MIT-MANUS (Interactive Motion Technologies, Watertown, MA, USA). (Figure 3.2) The InMotion2 is a planar module that provides two translational degrees-of-freedom for shoulder and elbow reaching movements. This configuration was selected because of its unique characteristics of low impedance on the horizontal plane and almost infinite impedance on the vertical axis. These characteristics allow a direct-drive back-drivable robot to easily carry the weight of the patient's arm, while allowing the child to express even weak attempts to move. Seating was individualized for each subject to provide the most comfortable conditions. The robot handle includes a cradle (Figure 3.3) so that patients with contractures or limited grasp could be well positioned to allow safe movement of the robotic arm.

Figure 3.2: MIT-Manus Robot

Figure 3.3: Hand Tray for MIT-Manus Robot

Clinical and functional evaluations

A battery of assessments was selected to afford a complete picture of the child's capabilities before and after (post-test and follow-up) therapy. Evaluations were administered by the same researcher at each session. Evaluators remained blinded to the subject's therapy group assignment throughout the course of the study. The assessments included:

Functional Measure:

1. The upper extremity portion of the modified Fugl-Meyer Assessment of Motor Function (F-M) to ascertain the subject's ability to accurately control various movements of the shoulder, elbow, forearm, wrist, and hand, as well as to test coordination and speed. The upper extremity portion consists of three sub-scales; one for shoulder, elbow and forearm function (score ranging from 0 to 40), the second for wrist and hand function (score ranging from 0 to 24) and the third to measure coordination and speed (score ranging from 0 to 6).

Muscle and motion capabilities:

1. The Modified Ashworth Scale[236] to assess tone of both the affected and unaffected arm.

2. Goniometric measurement of passive and active joint range of motion to assess muscle and motion capabilities.

3. Dynamometer measurement of grip strength. (JAMAR Hand-Grip Dynamometer, Sammons-Preston, Nottingham, NG, UK, SN# 30607574) to assess intrinsic hand strength.

Parent/caregiver feedback:

1. The self-care portion of the Pediatric Evaluation of Disability Inventory (PEDI)[237]. This survey is filled out by a parent or guardian and is designed to evaluate the child's functional skills. The scale is widely available and has standardized norms.

2. A parent survey to assess the child's activities and goals. There were two parts to this survey, "how well" and "how much" the child is using the paretic arm. This survey has been used in previous studies of robot assisted therapy in pediatric patients.[42,43]

Assessments

Pre-screening was done by interview with the child's parent, physician, and/or therapists. The entire battery of assessments was administered three times for each subject; the first no more than two weeks prior to the start of therapy, one within two weeks of the completion of the therapy protocol and, finally, six-months after completion. A brief medical history was taken during the first evaluation. Vision screening was used to assess oculomotor status and to screen for subjects who may not be able to follow on-screen computer cues.

Intervention

Children were randomly assigned to one of two therapy groups – sequential or random presentation using sealed envelopes opened after eligibility for the study was established. Sessions took place two times per week, separated by at least one day, until 16 sessions were completed. For each movement during therapy, the child attempted to move a robotic handle in order to move toward or away from a central target and eight peripheral compass-point targets. (Figure 3.4)

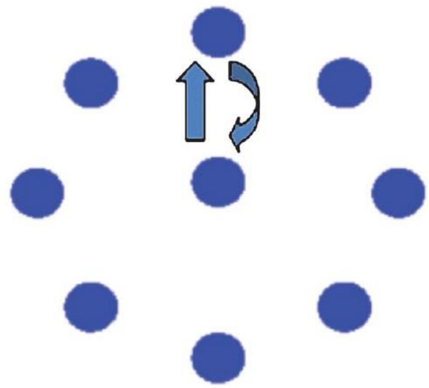

Figure 3.4: Peripheral Targets

Peripheral targets were presented around the circle in clockwise fashion starting at 12 o'clock for the sequential group and in an unpredictable fashion for the random group. During each session, the child performed three blocks of 320 repetitive, goal-directed planar reaching movements. Each block of 320 movements was broken up into four segments of 80 movements. Feedback in terms of knowledge of performance was provided after each 80 movement set. There were an additional 16 unassisted movements at the beginning of the session and after each block of 320 reaching movements. (These unassisted blocks of 16 movements are referred to as "One-Way Records"). Thus, there were a total of 1,024 reaching attempts with 960 "assist-as-needed" movements during each session; 480 being toward the central target (predictable for all subjects) and 480 toward the periphery (predictable for the sequential group, unpredictable for the random group). Each peripheral target was presented 60 times and was presented as cartoons to increase subject engagement. (Figure 3.5) Each therapy session took between 45 and 60 minutes.

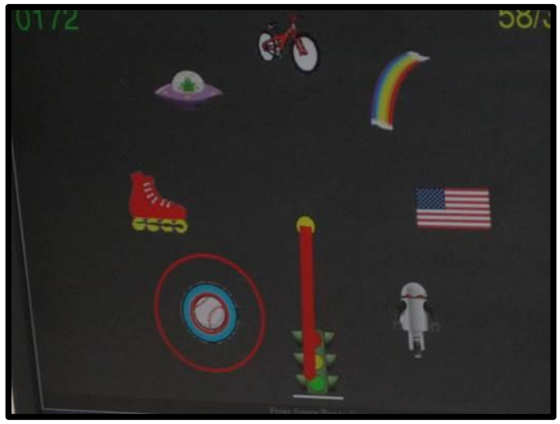

Figure 3.5: Intervention Display

Data Analysis

The MIT-Manus collects and stores kinematic data of subjects' performance automatically during each robotic session. Following completion of the research study, data was extracted from the MIT-MANUS for all subjects. Using Mat-Lab, data was organized to include only data that was collected during the One-Way Record activities; in which the patient was active and the robot passive. The data that was collected consisted of movements from the central target to one of the 8 peripheral targets. Each one-way record consisted of 8 of these movements. From this, average velocities were calculated for each one-way record performance. This resulted in 67 averages of data points per subject (1,407 overall for all subjects) for analysis. (Table 3.1)

Table 3.1: One-Way Record Collection

Study Stage	Number of One-Way Records Collected
Pre-Test	1
Intervention (16 sessions)	64
Post-Test	1
Follow-Up (6 mo)	1
Total	**67**

Movement time was chosen as the comparison variable to demonstrate improvement in functional ability. During One-Way Record tasks, subjects were instructed to move "as quickly as you can, while maintaining a straight line to each target". Following each One-Way Record, subjects were shown a visual representation of their performance in which the paths that they moved towards each target was represented. (Figure 3.6) Therefore, to the patient, there was an over-emphasis placed on producing consistent and accurate movements. The speed of each movement was then a secondary, non-emphasized variable and movement time could be attributed to functional improvement. Movement time was analyzed between subjects based on group characteristics and assignment. Additionally, potential improvements in movement times were examined over the course of intervention sessions, as well as within individual intervention sessions.

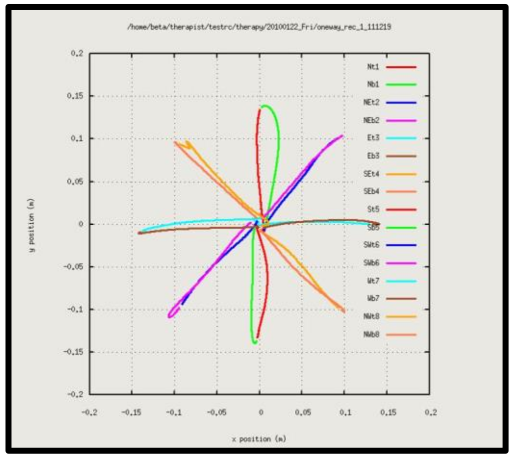

Figure 3.6: Example of One-Way Record paths

The statistics were computed with SPSS (version 24) to analyze the research questions. Groups were compared at baseline based on age and severity using independent samples t-tests to establish comparability between groups:

Research Question 1.1: Does task-specific, upper extremity robotic-assisted rehabilitation with targets delivered in a random presentation decrease movement time more than a blocked presentation in children with hemiplegic CP?

Analysis: A 2-way repeated measures ANOVA with a within subjects effect for time (Pre, post, follow-up) a between subjects effect for group (random vs blocked). Post-hoc analysis included pairwise comparisons with a Bonferroni correction applied.

Research Question 1.2 and 1.3: Does age affect movement time during upper extremity robotic-assisted rehabilitation delivered in both random and blocked presentations in children with hemiplegic CP? Does severity at intake affect movement time during upper extremity robotic-assisted rehabilitation delivered in both random and blocked presentation in children with hemiplegic CP?

Analysis: An ANOVA with a within subjects effect for time (pre, post) and with age and severity as random factors was calculated; the interactions (time by age and time by severity) were of interest.

Research Question 2: Do movement time changes in children with hemiplegic CP participating in robotic rehabilitation demonstrate an interaction between treatment day, treatment block, and/or treatment group to suggest an effect of dosing and intensity on outcomes?

Analysis: A univariate ANCOVA was run on the block difference data with treatment day, block, and group as fixed factors, and age and severity as covariates. Post-hoc tests outlined below were calculated to investigate the treatment day by block by group interaction.

Research Question 2.1: Do improvements in movement time over individual treatment days differ across the course of 16 treatment days suggesting an effect of dosing on improvements in children with hemiplegic CP participating in upper extremity robotic rehabilitation?

Analysis: A univariate ANCOVA was run on the block difference data with treatment day as a fixed factor, and age and severity as covariates. Pair-wise comparisons were computed to determine differences between treatment days.

Research Question 2.2: Is there a significant difference in movement time changes over each block of treatment during the course of 16 robotic-assisted training days suggesting an impact of intensity in children with hemiplegic CP?

Analysis: A univariate ANCOVA was run on the block difference data with block as a fixed factor, and age and severity as covariates. Pair-wise comparisons were computed to determine differences between blocks of treatment.

Research Question 2.3: Does the change in movement time improvements, each day, over the course of 16 treatment sessions of upper extremity robotic rehabilitation differ between those children assigned to a random presentation group and those assigned to a blocked presentation group?

Analysis: A univariate ANCOVA was run on the block difference data with group and block as a fixed factors, and age and severity as covariates. Pair-wise comparisons were computed to determine differences between groups.

Mitigation of Risk

Robotic devices are electrically actuated machines capable of independent motion, similar to that of a treadmill or isokinetic dynamometer, both of which are common rehabilitation tools. As such, they are capable of striking and potentially injuring the patient. To minimize the risk of this occurrence, multiple levels of protection were built into the machine. In the event of any malfunction, the servo-amplifiers are disabled within 2 milliseconds, removing power from the motors. At the same time, the kinetic energy of the robot's motion is dissipated by dynamic braking, which functions independently of any electronic components. Machine malfunctions are detected in several ways. Excessive speed, acceleration, or force exerted are detected by controlling software and result in disabling the system. An independent electronic circuit monitors the functioning of the software (via repeatedly reset digital output) as well as the motion of the robot, the availability of electrical power and the status of two-human operated “kill-switches”. Software failure, motion beyond a specified range, loss of electrical power, or activation of the switches all shut down the robot.

To prevent electrical fault from generating a potential hazard, all robot instrumentation, electronics and computer systems are powered by an isolated electrical supply equipped with a ground-fault detector and interrupt circuit. This equipment meets or exceeds electrical safety standards for operation in a clinical environment. This class of robots has been used daily for over 15 years with over 500 stroke patients at different rehabilitation hospitals. A 100% safety record has been achieved.

Chapter 4 : Results

Introduction

The following chapter presents the results from the secondary analysis performed on data from the original blocked vs random study of the MIT-Manus Shoulder Elbow. Results here are presented by research question. As discussed earlier, Research Aim #1 is a kinematic look at the questions posed by the original research study. That is, does training presentation and application of upper extremity, robotic rehabilitation impact movement times in children with hemiplegic cerebral palsy (CP). In contrast, Aim #2 investigates the impact of training structure (does and intensity) on upper extremity movement time in children with hemiplegic CP when participating in upper extremity robotic rehabilitation.

Participants

Twenty-one subjects met the inclusion criteria and were enrolled in the study. Of these, 16 subjects completed the intervention and all three assessments. All three subjects who failed to complete the 6-month follow-up had been assigned to the blocked presentation group. (Figure 4.1) Because of study attrition there were some variations in what data was analyzed for each of the research questions. Pre-, Post-, and Follow-up data were used in the analysis of Research Question 1.1. Only Pre- and Post- data were used in the analysis of Research Questions 1.2 – 2.3. Demographics of the study participants can be found in Table 4.3.

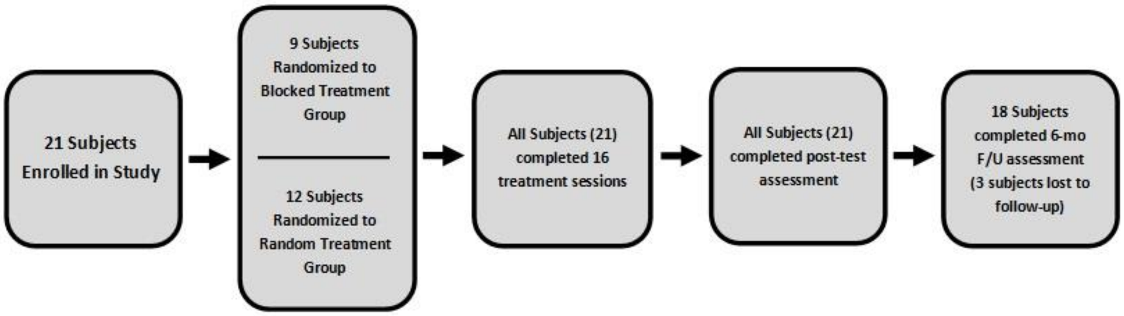

Figure 4.1: Study Participation

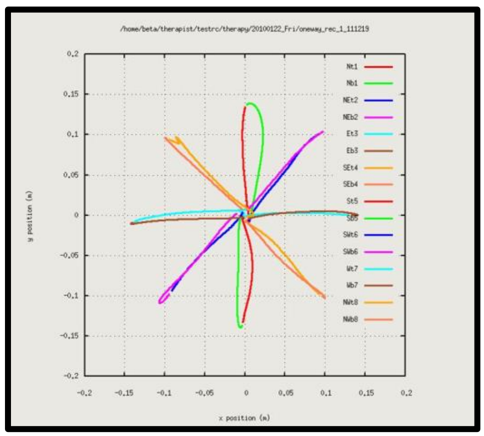

Figure 4.2: Example of a One-Way Record

<u>Data</u>

The data used for this analysis was derived from each subject's one-way record. One-way records are evaluation tools inherent to the Shoulder-Elbow MIT-Manus to assess a subject's ability to produce a star-like pattern without assistance from the robot. A single one-way record consists of sixteen discrete movement patterns, originating from a central target to one of eight peripheral targets and returning. Participants were instructed to move as quickly and smoothly (straight) to and from each target. Visual representations of each patient's movements were graphed for evaluator reference and for participant feedback. (Figure 4.2) Per the protocol, each subject was scheduled to complete 67 one-way Records over the course of the study (64 within the intervention sessions and 3 completed during outcome testing), providing a subject completed all intervention and evaluation sessions. This included each subject completing only one-way record during the pre-, post-, and follow-up evaluation sessions. In several cases, subjects completed more than one one-way record during the evaluations, bringing the overall average of one-way records completed during the protocol to 69.85. Additionally, two subjects completed less than 67 one-way records because of the subject's inability to complete all assessments on a particular intervention day. (Table 4.1)

Table 4.1: One-Way Record Completion

One-Way Records Completed:	
Total Number:	1467
Average:	69.85
Median:	71
Range:	59-75

The two groups were similar at the start of the intervention with slightly more participants in the random group. There was no significant difference in age ($T1,19 = -1.443$, $p = .08$) and severity ($T1,19 = 0.037$, $p = .97$) between the two groups. All 21 subjects completed all pre-test, intervention, and post-test sessions; however, 5 subjects failed to return for the 6-month follow-up assessment. (Table 4.2)

Table 4.2: Group Characteristics

Group	Gender	Age	Severity
Blocked	4 Male 5 Female	Range: 4-9 Average: 5.8 Stand. Dev. ±1.62	Range: 5-24 Average: 12.3 Stand. Dev. ±7.51
Random	7 Male 5 Female	Range: 5-11 Average: 7.3 Stand. Dev. ±1.95	Range: 4-25 Average: 12.41 Stand. Dev. ±6.41

Table 4.3: Subject Group Assignment and Demographics

Subject	Group Assignment	Gender	Age	FM Severity
1	Blocked	Male	7	11
2*	Blocked	Female	9	9
3	Random	Female	11	9
4*	Blocked	Female	7	7
5	Blocked	Male	5	6
6	Random	Male	6	6
7	Random	Male	9	18
8	Random	Female	5	5
9	Blocked	Male	6	20
10	Random	Male	8	25
11	Random	Male	6	16
12*	Blocked	Female	5	24
13	Blocked	Female	4	5
14*	Random	Male	6	19
15	Random	Female	7	8
16	Random	Female	5	13
17*	Blocked	Male	6	22
18	Random	Male	9	4
19	Random	Male	7	11
20	Random	Female	5	15
21	Blocked	Female	4	7
Totals:	9 Blocked 12 Random	11 Male 10 Female	Range: 4-11 Average: 6.6 SD: ±1.91	Range: 4-25 Average: 12.4 SD: ± 6.72

**Failed to complete 6-month F/U assessment* *SD= Standard Deviation*

Research Question 1.1

Does task-specific, upper extremity robotic-assisted rehabilitation with targets delivered in a random presentation decrease movement time more than a blocked presentation in children with hemiplegic CP?

Data analysis was performed utilizing repeated measures two-way ANOVAs, with pair-wise comparisons as a post-hoc analysis. No significant time by group interaction was found $F_{(2,28)} = .28$, $p = .62$. (Figure 4.3) However, a significant overall time effect was found for all subjects, $F_{(2,28)} = 4.83$. $p = .02$. The post-hoc analysis revealed that significant changes were observed for all participants pre to post-test (-1.25s, $p = .001$); pre-test to follow-up (-.76s, $p = .02$); but no significant difference between post-test and follow-up (+.49s, $p = .144$). (Figure 4.4)

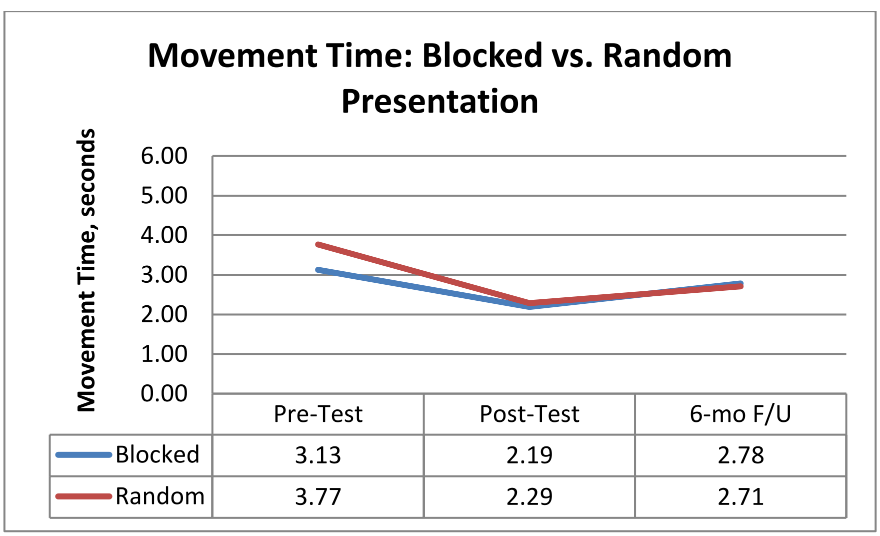

Figure 4.3: Movement Time: Blocked vs. Random Presentation

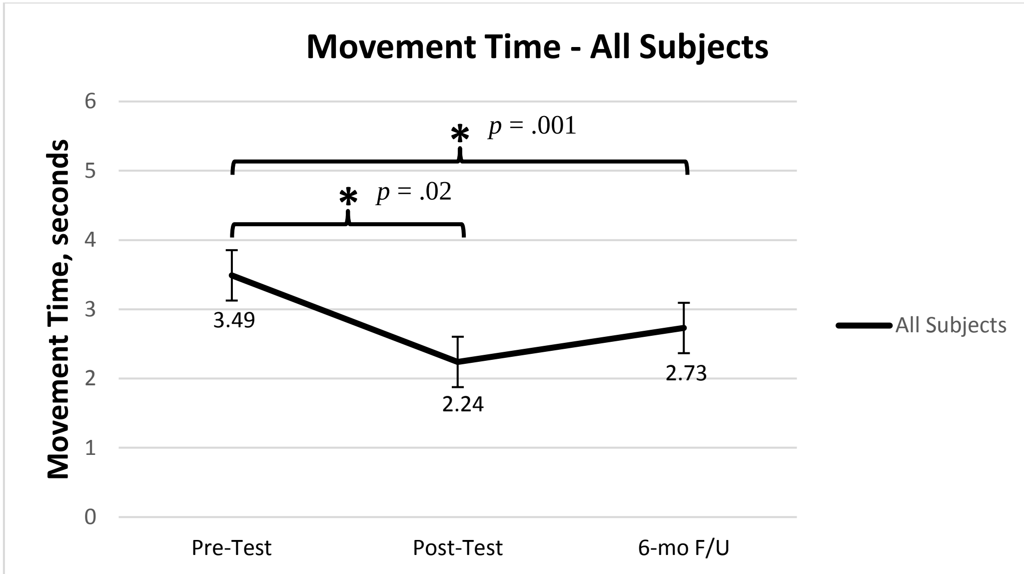

Figure 4.4: Movement Time - All Subjects

Research Question 1.2

Does age affect movement time during upper extremity robotic-assisted rehabilitation delivered in both random and blocked presentations in children with hemiplegic CP?

The age range for participants in the study was 4 years old through 11 years old. The two groups were similar at the start of the intervention with slightly more participants in the random group. There was no significant difference in age (T1,19 = -1.443, p = .08) and severity (T1,19 = 0.037, p = .97) between the two groups. All 21 subjects completed all pre-test, intervention, and post-test sessions; however, 5 subjects failed to return for the 6-month follow-up assessment. (Table 4.2) No significant age effect was observed in movement time due to age of the participants (F(1,18)= .315, p = .582).

Research Question 1.3

Does severity at intake affect movement time during upper extremity robotic-assisted rehabilitation delivered in both random and blocked presentation in children with hemiplegic CP?

The range of scores for the shoulder-elbow and wrist components of the Modified Fugl-Meyer Assessment (FM) at intake was 4 – 25. (Table 4.3) No significant time (pre-post) by severity interaction was found for movement times ($F(1,18) = .742$, $p = .40$). Individual FM scores were used in the statistical analysis; however, to illustrate this finding, subjects were divided into two groups and plotted based on intake FM severity, [More severe (n = 11) range = 4-9; Less severe (n = 12) range = 11-25] with the resulting plots remaining parallel with no interaction between the two groups. (Figure 4.5)

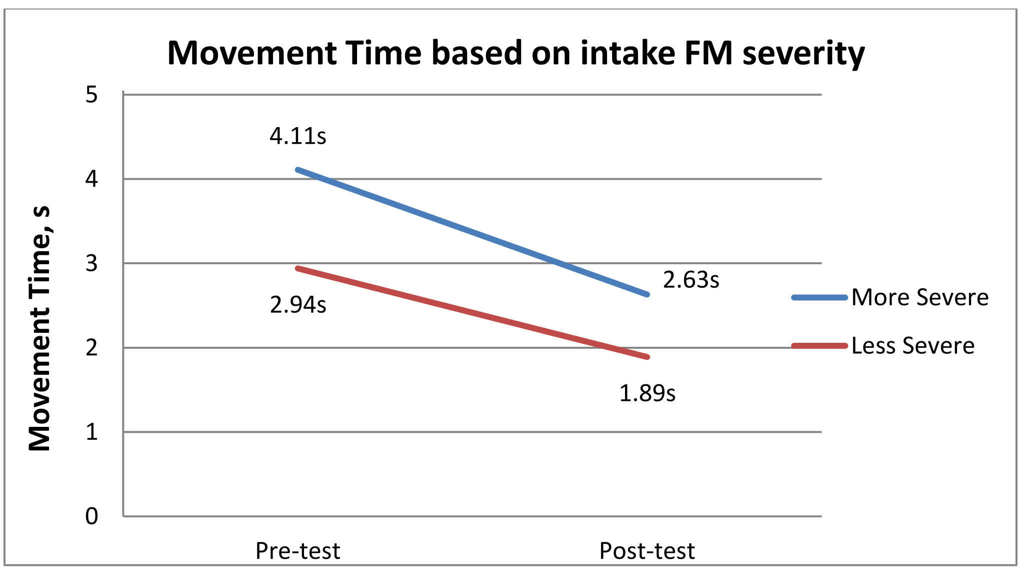

Figure 4.5: Movement Time based on intake FM severity

Research Question 2

Do movement time changes in children with hemiplegic CP participating in robotic rehabilitation demonstrate an interaction between treatment day, treatment block, and/or treatment group to suggest an effect of dosing and intensity on outcomes?

In Research Question #2 and its sub-questions, data is presented as block-difference (change) rather than movement time. An ANCOVA revealed an overall interaction between treatment day, treatment block, and treatment group, as well as an interaction between treatment block and treatment group. No interactions were found between treatment day and treatment block or between treatment day and treatment group. There was no significant main effect found in difference values with either age or initial FM when entered as co-variants. (See Table 4.4)

Table 4.4: Univariate ANCOVA

Univariate ANCOVA: Treatment Day | Treatment Block | Treatment Group		
Pairing	**F-Statistic**	**Significance**
Treatment Day | Treatment Block | Treatment Group	1.440	***.033****
Treatment Day | Treatment Block	.574	.967
Treatment Day | Treatment Group	.208	.999
Treatment Block | Treatment Group	3.416	***.025****
Co-variant: Age	.133	.715
Co-variant: Initial FM	.272	.602
		*P = 0.05

Post-hoc analysis for Research Question 2 will be discussed in the following sections, including the significant interaction found between treatment block and treatment group.

Research Question 2.1

Do improvements in movement time over individual treatment days differ across the course of 16 treatment days suggesting an effect of dosing on improvements in children with hemiplegic CP participating in upper extremity robotic rehabilitation?

There was no significant main effect found for treatment days ($F_{(15)} = .326$, $p = .993$).

Research Question 2.2

Is there a significant difference in movement time changes over each block of treatment during the course of 16 robotic-assisted training days suggesting an impact of intensity in children with hemiplegic CP?

During each treatment day (n = 16), participants performed 3 blocks of treatment. Each block of treatment consisted of 320 repetitions of movement. One-way records were collected at the beginning of each treatment day, between each treatment block and at the end of each treatment day creating four distinct time points in which to assess changes occurring during the preceding treatment block. (Figure 4.6) Data analysis revealed that differences existed in movement time changes between the three different blocks of treatment ($F_{(3)} = 5.471$, $p = .001$).

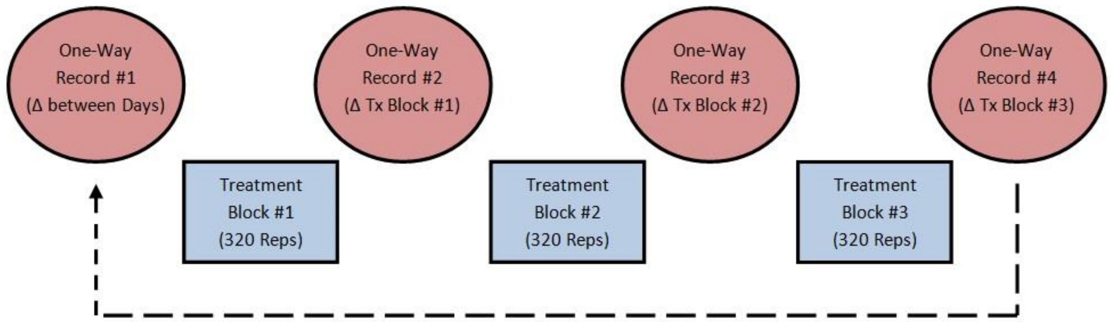

Figure 4.6: Daily Protocol

Average movement times for all assessments in a given block were compiled for all participants allowing a large number of samples (n = 1,310) to be compared (Table 4.5).

Table 4.5: Totals of One-Way Records

Assessment Point	**N**
One-Way Record # 1 (Δ between Days)	315
One-Way Record # 2 (Δ Tx Block #1)	335
One-Way Record # 3 (Δ Tx Block #2)	331
One-Way Record # 4 (Δ Tx Block #3)	329

Pairwise Comparisons were used to examine the changes in average movement time over each block at each of the evaluation points (One-Way Records), indicating the impact of the treatment block that proceeded the evaluation point. Post-hoc analysis revealed that the average difference in movement time for One-Way Record #1 (Δ between Days) was significant with a mean difference of .288s, indicating that, on average over the course of 16 treatment sessions, participants returned for their next session and initially performed *slower* than they had performed during their final evaluation on the preceding treatment day. One-Way Record #2 (Δ Tx Block #1) and One-Way Record #3 (Δ Tx Block #2) were not significant. One-Way Record #4 (Δ Tx

Block #3) was significant, while the difference for One Way Records #3 and #4 were not. (Table 4.6)

Table 4.6: Pairwise comparisons of assessments following treatment blocks

	Mean Difference (A-B)	**Significance (*P*=0.05)**
Treatment Block #1	.098	1.000
Treatment Block #2	-.014	1.000
Treatment Block #3	.204*	***.032***
Between Treatment Days	-.288*	***.001***

Research Question 2.3

Does the change in movement time improvements, each day, over the course of 16 treatment sessions of upper extremity robotic rehabilitation differ between those children assigned to a random presentation group and those assigned to a blocked presentation group?

Based on Research Question #2 and the Block | Group interaction (See Table 4.4), a post-hoc analysis was performed to further investigate the effect of group assignment to changes in movement times over each block of treatment. Based on the overall interaction, an ANCOVA was re-run using only treatment group and treatment block, with age and initial FM scores remaining as co-variants (treatment day was excluded), revealing a significant main effect (F = 5.204, p = .002). As a post-hoc analysis, individual One-Way ANOVA's were calculated for each block, indicating a significant difference in average movement time changes between treatment groups for One-Way Record #1 (Δ between Days) (F = 7.291, p = .007) and One-Way Record #2 (Δ Tx Block #1) (F = 4.667, p = .031). (Figure 4.7)

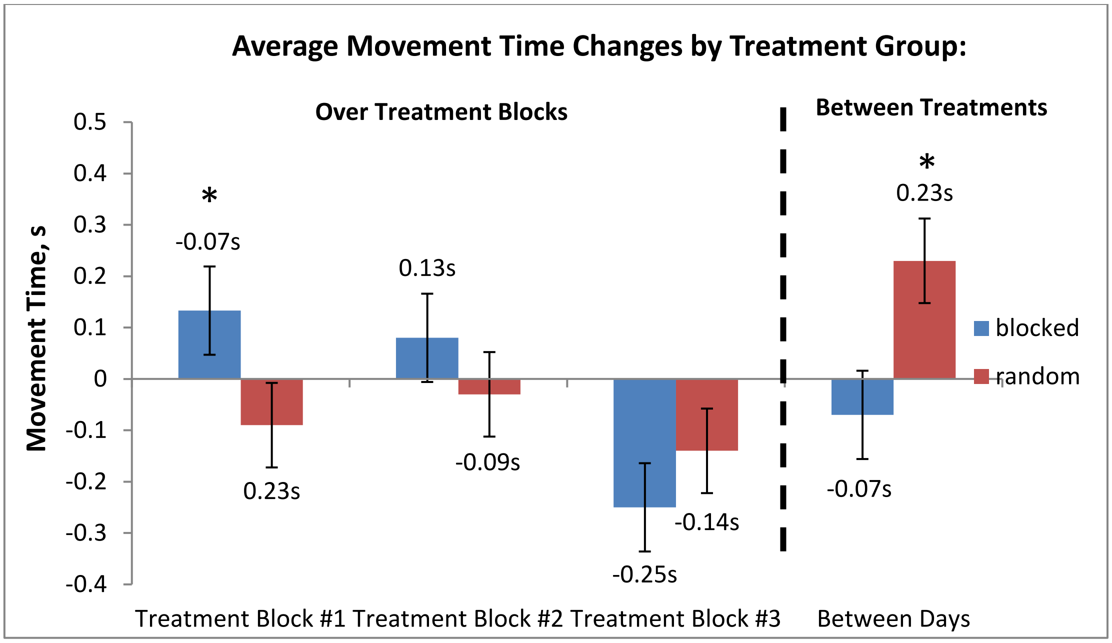

Figure 4.7: Movement time changes over treatment block by group

Chapter 5 : Discussion

Introduction

The data for this investigation was derived from a previous study[29] that investigated the impact of variations in target presentation during upper extremity robotic rehabilitation in children with hemiplegic cerebral palsy (CP). As reported earlier in Chapter 2, the original study found no significant difference between target (sequential and random) presentation, but did find an overall improvement in clinical outcomes over the course of the intervention as compared to baseline for all participants of robotic training.[29] (See Table 5.1 for a summary of these results) In addition to the clinical results, investigators conducting the study received anecdotal reports from parents of participants regarding improvement in functional skills such as: beginning to use affected upper extremity with utensils when eating and being able to don/doff pants adequately enough to allow independent toileting at school. While the original study was not designed to capture these reports as part of data collection, they nonetheless represented significant improvements in function for the participating children. Despite the clinical outcomes demonstrating no statistical significance between the target presentation groups, participants appeared to experience impactful functional change resulting from their participation in robotic training.

Table 5.1: Selected outcomes from original study (Mean, Standard Deviation)

Measure	Group	Pre-Test	Post-Test	6-mo F/U
PEDI self-care	Random	64.0 (12.24)	70.4 (12.14)	70.0 (15.94)
	Sequential	68.13 (22.8)	71.3 (21.9)	71.6 (21.1)
Ashworth	Random	5.3 (3.3)	3.5 (2.4)	2.9 (2.3)
	Sequential	5.3 (3.9)	3.7 (2.4)	4.4 (3.3)
Fugl-Meyer	Random	21.7 (12.6)	23.8 (14.5)	25.8 (15.8)
	Sequential	19.0 (11.0)	22.8 (14.0)	23.5 (13.9)
Fugl-Meyer proximal	Random	11.4 (5.9)	12.5 (7.0)	13.8 (7.8)
	Sequential	9.6 (5.0)	11.8 (6.2)	13.7 (5.8)

Many questions arose regarding the study design in response to the lack of findings differentiating blocked and random target presentation. In addition to questions about whether the outcomes analyzed were reflective of the motor capacity improvement, questions about implementation were also extensive:

- Was the frequency of intervention sessions sufficient?
- Should the children have completed more repetitions per session?
- Should they have completed less?
- Were intervention targets displayed appropriately on the robotic device?
- Did we choose the correct outcome assessments to capture the motor changes occurring through intervention?

Similar questions are common for nearly all completed clinical research studies; however, because the original study was completed on the MIT-Manus Shoulder-Elbow Robot, we possessed the ability to re-examine questions from a new perspective. The current study used clinical outcome data obtained from the original study to further establish the effectiveness of the robotic intervention. Rehabilitation robotics have potential utility to improve outcome assessments because of their ability to capture markers of performance in real-time through kinematic data. The kinematic data allowed for a more comprehensive, and potentially more sensitive, view of motor changes throughout the study and may illustrate why participants demonstrated improved motor capacity as reported by parents. As it was reported in Chapter IV, the kinematic data allowed the exploration of mechanisms behind the clinical changes observed in the original study and to quantify motor changes occurring in children participating in upper extremity robotic training that resulted in the positive anecdotal reports received.

Rehabilitation Robotics as Outcome Measures to Evaluate Dosing

Traditional rehabilitation studies, including our original study design, are limited by the scope of the outcome measures they employ and by the time points in which those measures are performed. Previous upper-extremity robotic literature has suggested that the lack of sensitivity and/or the lack of appropriate measures to test the skills being trained by an intervention may have limited the reportable benefits of robotic training.[11,29,43,110,114,179] Because humans are largely bi-manual, many outcome measures designed to capture upper extremity function utilize both upper extremities, making it difficult to properly address improvements in functional tasks following upper extremity interventions. Dual upper-extremity tests often fail to distinguish the benefits of an intervention applied to only one arm, as is the case with robotic therapy interventions for a hemiplegic population. Available tests that do address a single upper extremity may not be sensitive enough to capture changes in a non-dominant upper extremity and highly adaptable children will be inclined to utilize their non-affected extremity for daily tasks. Even with functional improvement from an intervention protocol, these tests may either allow for compensatory movements that prevent isolated assessment or fail to capture minute changes that occur in the affected extremity. Beyond this, many task-based upper extremity assessments; including the Action Research Arm[238], Frenchay Arm Test[239], Peg Tests[240], Rivermead Motor Assessment[241], and Motor Assessment Scale[242], function based on whether a patient "can" or "cannot" perform an activity. As such, these assessments lack the sensitivity to detect or account for partially completed movements and, therefore, fail to provide information about the patients strategy and reactions during the test.[243]

The main upper extremity assessment that was used in our original research design was the Fugl-Meyer scale,[223] which is a more comprehensive and potentially discriminatory upper extremity assessment, composed of ordinal scales for sensation, proprioception, joint pain, range of motion, reflex activity, and joint coordination. However, the individual components making up the Fugl-Meyer do not assess purposeful reaching tasks nor do they quantify the functional impairments that are present due to spasticity or weakness.[243]

Another limitation of clinical outcome measures is the timeframe in which they are performed. Traditional rehabilitation studies utilize a pre-test/post-test format; potentially, with follow-ups at defined periods to capture long-term outcomes. This format does well to examine clinical changes that occur over the entire duration of an intervention plan, but cannot identify at which point during an intervention performance changes occurred. Outcome measures can be included at certain time points throughout an intervention to attempt to capture ongoing changes, but this adds additional length to the study protocol and potentially introduces a testing effect which impact overall outcomes as participants become familiarized with the testing protocol.

Because of these limitations, the ability of robotics to combine real-time kinematic data with a traditional outcome measure assessment protocol has the potential for more descriptive data that can show incremental changes in performance that do not reach the threshold of standard outcome measures. Additionally, robotics offers an unbiased view of performance. Whether outcomes are being examined within individual sessions or over the duration of a training protocol, robotics provides objective measures of participant performance that are blinded to all other external variables. More so than simply the researchers, the innate ability of robotics to capture data in the "background" during intervention sessions renders the participant unaware of assessment. Therefore, there is no risk of altered performance due to the awareness of being tested.

Within the MIT-Manus Shoulder-Elbow robot, there are many data points available to utilize for kinematic analysis that are readily provided to the researcher or clinician during an intervention session, which include: robot initiation, robot power, distance from target, distance from straight line, and motion jerk. (Figure 5.1) These measures are automatically produced at the end of each block of 320 repetitions and serve as excellent summaries to assist clinicians in their patient's performance during training. However, by extracting the raw kinematic data that is collected in real time (and that is used to formulate the summary screen), we are able to calculate more specific assessments of subject performance. These measures are summarized in Table 5.2. Appropriate and fruitful questions could have been derived from any of these available data sets and, speaking again to the evaluative power of rehabilitative robots, may be accessed again in the future for further study. However, for the purposes of this analysis, we chose to focus on movement time to discrete targets, specifically, the time it took for a participant to move from the central "starting point" on the visual array to one of the eight peripheral targets.

Figure 5.1: Available data points (in-session)

Table 5.2: Available Assessments from derived Kinematic Data

Time	The amount of time, in seconds, for a participant to move from the center target to the 8 peripheral targets.
Path Length	The length of the path, in meters, that a subject made while completing a movement from the center target to the 8 peripheral targets.
Path Ratio	The length of the path, in meters, divided by the end position of the reach.
End Distance to Target	The distance, in meters, from the target to the end position of the reach.
Peak Velocity	The highest velocity, in meters per second, which a participant reached while moving from the center target to the 8 peripheral targets.
Peak Acceleration	The highest acceleration, in meters per second squared, which a participant reached while moving from the center target to the 8 peripheral targets.
Time to Peak Velocity	The time, in seconds, from initiation of movement at the center target until the participant reached his or her peak velocity along the path toward a peripheral target.
Time to Peak Acceleration	The time, in seconds, from initiation of movement at the center target until the participant reached his or her peak acceleration along the path toward a peripheral target.
Number of Movement Units	The number of zero acceleration crossings indicating discrete sub movements that a participant made while completing the path of movement from the center target to a peripheral target.

Fitts' Law

The movement time data was captured during each subject's one-way records, when the robot was in a passive mode and the subject was responsible for producing all movement. Instruction during this activity was to move towards each target as it illuminated, maintaining as *straight of a path as possible.* Because of the over-emphasis on creating a straight path (no verbal instructions were given relative to speed), we can assume that improvements in subjects' speed during this task (decreases in movement time) are the result of improved functional ability. Visually, subject's one-way records improved in their consistency and order over the course of treatment sessions, as movement times decreased. (Figure 5.2) Very simply, speed (velocity) is the rate that an object moves a particular distance over a given time ($v = d/t$).[244] While it is possible that subjects in this study could have increased speed over a longer path, the overall trend of decreased movement time throughout the training and the visual evidence of straighter paths on the one-way records suggest otherwise. The decrease in movement time may then be attributed to one or more of several factors, such as improved initiation, improved coordination, improved synergistic patterns, improved strength, reduced impact of spasticity, or improvement on the task itself. While kinematic data derived from the robot cannot distinguish which of these factors is responsible for improvements in movement time, it is known from the original study that clinical improvements over the course of treatments were observed in: coordination and synergistic patterns (Fugl-Meyer) and spasticity (Modified Ashworth). (Table 5.1)

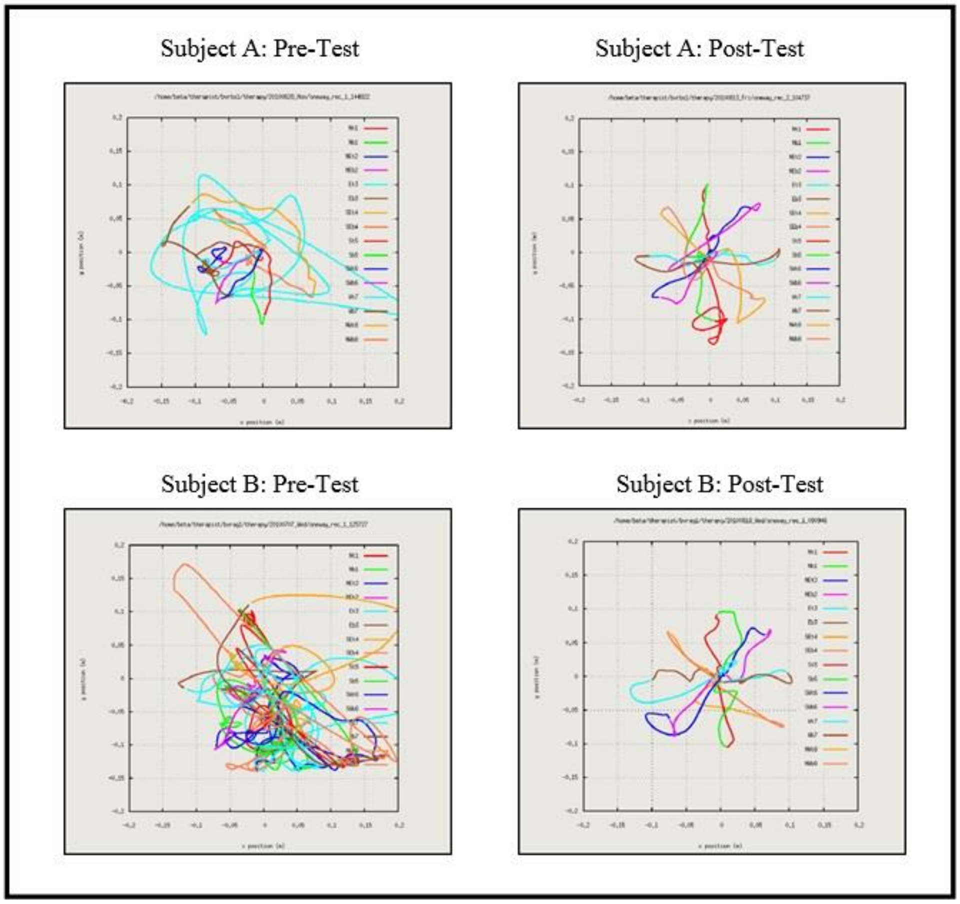

Figure 5.2: Sample One-Way Records (Pre-test, Post-test)

This comparison can be supported through the application of Fitts' Law, which is the relationship between movement speed and accuracy during reaching whereas an increase in accuracy is related to a reduction in reaching speed.[245] In and of itself, upper extremity reaching is a complex process in which segments of the upper limb move about seven possible degrees of freedom (i.e. joint rotations), in the shoulder, elbow, forearm, and wrist.[246] This excess of joints affords the central nervous system the ability to employ an infinite number of strategies when reaching towards a specific target.[247] In normal, unimpaired humans, this biomechanically based movement is associated with a velocity profile that is characterized by a bell-shaped curve in which peak velocity occurs approximately halfway between the start and end-points. Peak velocity corresponds to the changeover from the acceleration to deceleration phase, and its location within the velocity profile is an indicator of the person's strategy. However, as the requirements for accuracy increase, the bell-shaped velocity curve becomes skewed with peak velocity occurring earlier in the movement. Conversely, as requirements for speed increase, peak velocity occurs later in the movement task.[243]

Decreases in accuracy during upper extremity movements are caused by the reduced coordination of the shoulder and elbow joint movements.[248] For individuals who have neurological impairment, reaching can be affected by many factors including: spasticity, decreased range of motion, coordination difficulties, weakness, and/or decreased central motor recruitment.[249] While these impairments will affect both accuracy and speed during reaching, research has shown that those with neurological deficits follow similar patterns as un-impaired subjects. Krebs et al. used kinematic analysis of hand paths to track recovery of patients who had suffered a stroke during unconstrained reaching tasks. Not only did the group find improvements in both accuracy and smoothness, they also found a re-acquisition of the bell-shaped velocity profile following 11 weeks of training.[250]

Additional studies have found that movement kinematics were more optimal when participants reached in synchronization with an external rhythmic stimulus[251], and that altering instructions from an external focus to an internal focus during training changed reaching kinematic outcomes.[41] The results of these studies suggest external factors such as therapist's instructions, as was done in our study, can positively affect motor performance.

Massie et al, conducted a study in 2012 that found stroke survivors to be able to alter their hemi-paretic reaching behavior when switching between a self-selected reaching pace and a fast reaching pace. In this study, the demands on the participants for accuracy where held constant, yet those performing the fast pace reaching tasks experienced the greatest improvement in kinematic variables.[252] This study supported earlier findings by Lin, et al. who found that increased speed requirements optimized movement strategies in stroke survivors reaching with their less-affected extremity.[253]

The application of Fitts' Law to the current study can be made in reverse to support the assumption that a decrease in movement time is indicative of improved overall functional ability. The literature reported thus far in this section suggests that with active focus on speed, kinematic factors improved as subjects' speeds increased. Over-emphasizing accuracy resulted in movement time improvements becoming a bi-product of improved kinematic variables in our subjects, such as coordination, initiation, strength, and movement control.

Overall Impact

Similar to the clinical outcomes of the original study, the current study found no overall difference in movement time between those receiving training through a blocked presentation of targets and those receiving training through a random presentation of targets. However, an overall improvement in movement time was found when combining groups and examining the sample as a whole; movement time decreased an average of 1.25 seconds (36%) from pre-test to post-test ($p = .001$) and an average of .76 seconds (22%) from pre-test to follow-up ($p = .02$). Within this study sample, there was relative homogeneity in age and severity (Table 4.3) between the “blocked” presentation group and the “random” presentation group.

Accepting decreases in movement time as indicative of “improvement”, these results suggest that task-specific upper extremity robotic rehabilitation on the MIT-Manus Shoulder-Elbow robot was an effective treatment strategy for children with hemiplegic CP, but that target presentation may or may not be a contributor to that effect. This conclusion follows previous studies of robotic rehabilitation[29,31,40,42,45] that all found improvements in outcomes for children with CP participating in upper extremity robotic training, despite various protocols utilized.

Training Effect vs Learning Effect

The goal of all rehabilitation strategies should be to create a lasting functional improvement in patients. A training effect is an immediate improvement in performance experienced as the result of practice. Typically, the training effect diminishes over time if the task is not repeated. Successive training, resulting in cumulative training effects can then lead to learning. When something has been learned, be that a physical task or cognitive function, we anticipate that the learning is permanent and can be recalled or repeated on demand.[254] Relative to the robotic intervention in this research study, the difference between training effect and learning is crucial. For robotics, and in this case, our particular protocol on the MIT-Manus Shoulder Elbow robot, to be worthwhile, the results from training must be maintained long after the intervention ceases.

Kleim[255] reports that the development of motor skill is characterized by two general phases of learning. The first involves rapid improvements in performance that can be observed in both single training sessions and across the first few sessions of an intervention. The second phase then involves slower gains in improvement.[90,92,94,256] This can be seen in the data from this study (particularly in the more severe intake group) as movement speeds improved more rapidly over the first 5-6 sessions before slowing and maintaining a more steady rate of improvement (Figure 4.4).

Neural imaging studies have demonstrated that these two phases of motor learning are represented by different patterns of activity across the motor system.[94] The initial phase involves activation of the striatum and cerebellum, while the latter phase is represented by activity in the motor cortex.[140] It has also been reported that changes in cortical synapse number are only detectable during the late phase.[256] This suggests that motor map reorganization (motor cortex) occurs during the late, rather than early, phase of motor learning.[255]

Movement time for all participants in the study improved significantly from both pre-test to post-test and from pre -test to follow-up. A non-significant increase in movement time (0.49s) occurred from the post-test session to the follow-up at six months post-intervention. As motor skills require maintenance and context to remain intact,[257] this non-significant decline from post-test to follow-up is expected. The children who participated in the study completed 1,064 repetitions of similar movement over the course of 16 treatment sessions; over 17,000 repetitions of movement per subject. Following 6 months of no practice, the decline in performance is likely representative of a training effect dissipating over time. The encouraging results from this study were that children maintained a significant improvement in movement time at the 6-month follow-up as compared to their pre-test. The retention of the specific motor skills necessary to complete the one-way record, without the context of the robotic environment over that time, is indicative of motor learning and permanent change.[257,258] Further, the basic science in the field of neuroplasticity has supported the concept of cortical reorganization to account for improved or regained motor skill following neurological injury.[77,88-92] The retention of motor skills that were previously unknown over a 6 month period of no practice would suggest that cortical reorganization had occurred. While imaging studies would be required to confirm, the permanency of the skill in participating children is similar to the functional results from previous neuroplasticity studies[83,86,92] and supports this assumption.

Regarding the efficacy of the robotic intervention, even more encouraging is that the participants experiencing the permanent motor skill changes are children with CP, who are susceptible to changing physical limitations and secondary impairments as their bodies grow and develop. In a child, significant maturation can occur over any six-month period. For children with CP, maturation is typically accompanied by changes to their secondary impairments; such as fluctuations in tone and changes to contractures/muscular extensibility. That the follow-up scores for these children remained significant as compared to pre-test assessments is encouraging that the robotic intervention may indeed be intensive enough to produce change above these natural impediments.

Another indicator of motor learning is the successful transfer of skills learned in one task to that of another unique task.[259] All data collected during this research trial came from one-way records. As described previously, one-way records are collected in an environment identical to that in which the intervention occurred. The only difference between the one-way record data collection and the intervention is the absence of assistance from the robot itself. Therefore, an argument could be made regarding the use of one-way record data as an indicator of motor learning. Because the task completed is not novel, there may be a skewed training effect masquerading as learning. Children who participated in this research study also completed a series of circle-drawing tasks on the MIT-Manus Shoulder-Elbow robot. The circle assessments were completed at pre-test, post-test, and 6-month follow-up. The circles represent a novel task as all intervention movements were performed in a linear manner and no practicing of circles occurred during the 16 treatment sessions. Therefore, improvement in circle drawing can be used as another indicator of motor learning, as the improvements made on one-way records are transferred to the novel task.[259] Although no kinematic data was extracted to compare circle drawing performance, we can visually compare results to note a marked improvement following training. (Figure 5.3)

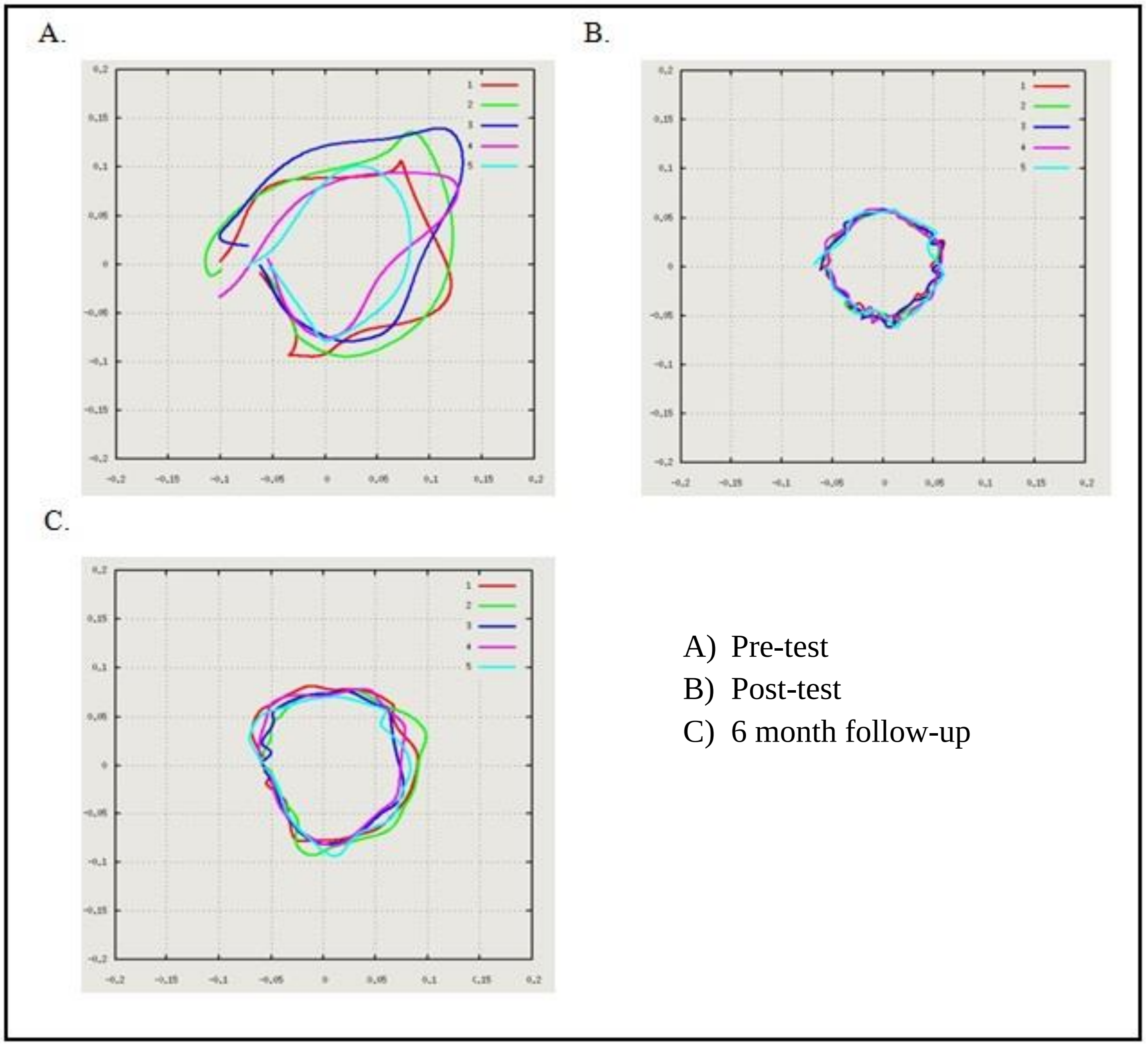

Figure 5.3: Schematic graphs of a participant's circle assessments

Dosing

Rehabilitation Robotics utilization allows for performance to be “sampled” throughout an intervention protocol. This ability to gain snapshots of changes in performance, through kinematic data, over the course of treatment can provide valuable insight into questions on dosing; giving researchers and clinicians’ data to consider when determining frequency, intensity and duration of interventions for future research or clinical application. In our original study, children performed 1,080 repetitions each day, two times per week, for eight weeks. Based on the overall positive response of children to robotic intervention, we immediately began work on a follow-up pilot project to examine functional outcomes in children who performed either 320 or 640 repetitions per intervention session at the same frequency as before. Data from this study has yet to be published, but preliminarily findings suggest little differences in the clinical outcomes of these two intensities as compared to the original study dose.

The initial kinematic analysis of this data produced similar overall results of pre-test to post-test outcomes as to the original clinical outcomes; however, analysis of the kinematic data revealed variances that were previously unseen. A univariate ANCOVA revealed a significant treatment interaction was present between treatment day, treatment block, and treatment group. Subject age and severity were assessed and determined not to significantly impact group performance. Analysis found that the significant interaction was between treatment block and treatment group, indicating that an important criterion of establishing dosing for upper extremity robotic rehabilitation in children with hemiplegic CP was: A) number of repetitions performed in a given treatment day, B) presentation group (blocked vs sequential) relative to repetitions, or C) both.

An early hypothesis when first collecting this data was that improvements in movement time would plateau at some point during the intervention. Considering the age range of the population for this study (4-11 years), it was predicted that children's attention spans would naturally wane after such a high number of repetitions within a rote task. This was not particularly concerning as animal models have previously suggested that 400 repetitions is a sufficient amount of practice of a singular task to produce cortical change.[108] Anecdotal evidence of subjects' engagement during the training test did not discount this assumption. Children completed the intervention session of 1,064 repetitions in times ranging from 35 to 75 minutes, with the range resulting from various factors including severity, motivation, cognitive ability, concentration, and mood. Regardless, patients were generally happy to be finished with the intervention, giving the impression that attention waned during later repetitions.

It was therefore surprising to find that the greatest improvements in movement times between two one-way records occurred over one-way records #3 and #4. Over the course of 16 treatment sessions, the change score between one-way record #3 and #4 was .204 seconds faster (p = .032). Improvement occurred within all three blocks of treatments over the course of the protocol, though non-significantly during blocks #1 and #2. These results suggest that the greatest gains in movement time were found during block three; that is, repetitions 640 – 960 of the intervention protocol.

This finding highlights the potential power of robotics as assessment tools for research. Based on previous literature and the clinical data from the original study, our initial reaction to the positive, yet non-significant results, was to design a follow-up study with fewer repetitions. Our biases, though based on sound reasoning, did not immediately lead us to consider that children may benefit from more than 1,084 repetitions of movement. The ability to look at changes occurring within the intervention protocol demonstrated a much different response. Not only did the subjects improve during the final block of treatment, it is where they experienced the biggest gains.

Rehab Effort

Dosing typically refers to the intensity and duration of clinical intervention.[14] These measures provide information about the amount of intervention (minutes and/or days of week), but fail to capture the number of repetition or practice within a particular session.[260] Given the contemporary clinical belief that more practice is better[14], it is important that we utilize the proper framework of intensity in designing intervention studies with a focus on practice within actual therapy time rather than a scheduling vernacular.

In 2007, Lang, MacDonald, and Gnip[260] published a study of observational data on activity during rehabilitation sessions in the Rehabilitation Institute of St. Louis. Lang and her colleagues discovered that the average session duration across 36 Physical Therapy and Occupation Therapy out-patient sessions was 36 ± 14 minutes. (This was the number of actual active minutes within each therapy session, and not a representation of a particular patient's scheduled treatment time.) For patients receiving upper extremity based rehabilitation, Lang and colleagues found that the number of purposeful movements during an average intervention session ranged from 5.4 -18.6, active-exercise movements ranged from 20.1 – 57.5, and that passive-exercise movements ranged from 20.2 – 47.5.[260] Gleaned from the data presented in Lang's study, a patient participating in upper-extremity based rehabilitation performed on average 45.7 – 123.6 movements in a given session. This number, representing usual care in clinical settings, is significantly lower than the numbers of repetitions performed in animal plasticity and human motor learning studies.[86,90,92,106,261]

One of the most potentially beneficial aspects in the utilization of robotics within a rehabilitation protocol is the ability to mass high amounts of repetitions within time frames similar to that of conventional therapies. As Lang's data suggests, perhaps it is not the timing of intervention performed, but the amount of active practice performed, regardless of distribution. "Rehab Effort", presented in Chapter 1 (Figure 5.4) as a conceptual framework for this dissertation, attempts to provide a method for looking at dosing through the lens of overall participation, rather than scheduling logistics.

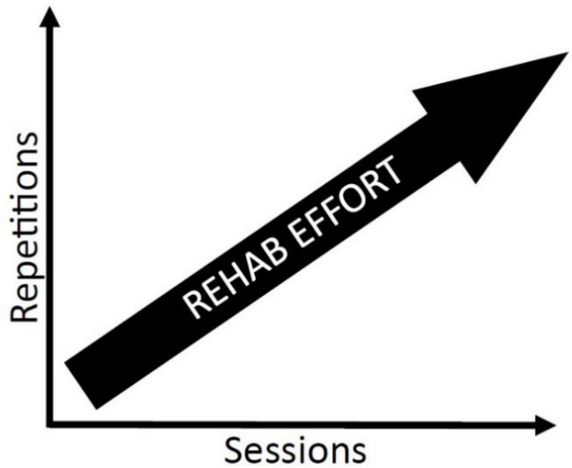

Figure 5.4: Rehab Effort Conceptual Framework

Rehab Effort suggests that repetitions are cumulative in nature. That is, the impact of practice can be realized through increasing repetitions both within sessions and over the course of successive sessions. Drawing on the conclusions of both animal models and human motor learning models presented earlier[86,90,92,106,261], we find that it is imperative to design intervention studies at a level of practice adequate in intensity if we are to expect similar results in our impaired patient populations.

Applying the Rehab Effort framework to a singular treatment session of robotic intervention, we find that the cumulative effort rises as the session progresses. (Figure 5.5) It is self-explanatory that with each successive treatment block, the amount of repetition experienced by the subject is increased. To this point, as we stack successive treatment sessions together (Figure 5.6), we see that the cumulative number of repetitions undertaken over time continually increases. It is a subtle, yet potentially important, distinction to look at total repetitions of movement over the *course* of a treatment protocol rather than focusing on repetitions per session and number of total sessions. As Kleim's work earlier in this section suggested, cortical reorganization likely occurs in the later phase of motor learning.[255] While not conclusive, our data suggests that participating children experienced greater decreases in movement time in the latter stages of each treatment session; and continued to decrease movement time throughout the study. It is possible that it is not the presentation of repetition that matters (i.e. dose), but rather the total amount of repetition that ultimately leads to motor gains.

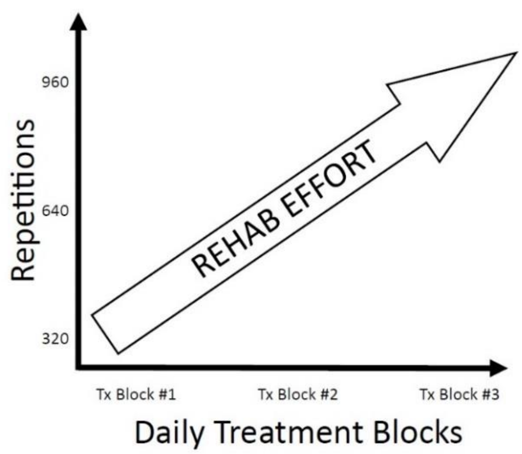

Figure 5.5: Rehab Effort depicting repetitions within a single treatment session

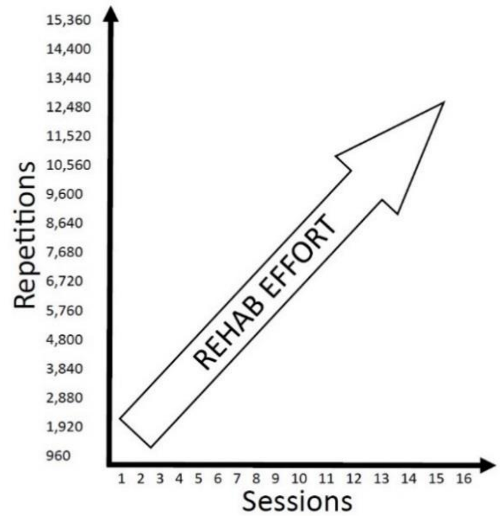

Figure 5.6: Rehab Effort depicting repetitions over multiple sessions

While an untested theory at this point, the implications of the successful application of this conceptual framework of rehabilitation effort are far-reaching in both the research and clinical realms. From a research perspective, the Rehab Effort clinical framework provides a means for collecting data through true clinical trials rather than through pre-designed research protocols. In the absence of concrete knowledge regarding the correct dosing and structure for an intervention in any given diagnosis pool, rehab effort offers a framework to organize otherwise unstructured, “messy” clinical data. Clinicians can treat patients based on their clinical judgement, progressing patients as they see fit, unencumbered by a research protocol. If the amount of practice that each of their patients participates in is recorded, it can then be plotted against outcomes to determine the rehab effort required to achieve those outcomes, regardless of schedule.

Presumably, this model allows researchers a fresh perspective towards clinical data with the ability to utilize similar, though not equal, patient pools and treatment approaches. The gold-standard of research is, and will remain, randomized controlled trials (RCT). By their design, the weaknesses of RCT’s is that they are costly, restrictive in their inclusion criteria, and strict in their administration of treatment protocol. Utilizing clinical data within the Rehab Effort conceptual framework allows researchers to be less focused initially relative to inclusion and exclusion considerations and collect more diverse research that is applicable clinically and can then serve as the structure for RCT's.

Clinically, Rehab Effort may provide a bridge in which research protocols can be translated into clinical practice. The double-edge sword of research is that far-too often, the protocols that are established within highly effective studies are not practical for traditional clinical use. While sound in science, they fall apart when faced with the realities facing clinicians today: insurance regulations, patient preference, patient schedule, clinic availability, etc. Clinicians must balance their desire to practice evidence-based care with the realities of providing treatment in today's healthcare environment. The application of the Rehab Effort conceptual framework would allow the clinician to focus less on the structure of a research study's protocol, and instead attempt to replicate the total effort.

For example, if a body-weight supported treadmill training study found favorable results for post-CVA patients when completing 5 sessions per week for 3 weeks, a clinician could use the framework of rehab effort to modify the dosing structure to accommodate his or her patient's needs. The protocol from the study consisted of 15 sessions. If a patient's insurance will only allow a maximum of 3 sessions per week, the therapist can extrapolate the study's finding by scheduling their patient for 5 weeks, at 3 sessions per week, rather than 3 weeks.

Further, if the research study published repetitions, that is, the amount of actual steps that the subjects had performed during the body-weight training protocol (e.g. 1,000 steps per session; 15,000 over the entire protocol), a clinician would have even more flexibility to accommodate a patients schedule by working over the course of successive sessions towards the target of 15,000 steps. Utilizing the conceptual framework to this degree allows clinicians to also accommodate a patient's changing performance throughout recovery. It is likely that fewer steps will be realized early in the protocol and the patient will be able to perform more steps per session later in the protocol. The clinician can modify their dosing for the patient as they work toward the target number of cumulative steps.

The same conceptual framework can be applied from the results of this secondary analysis. The subjects in this study completed 16 sessions (2 sessions/week x 8 weeks) of robotic-assisted upper extremity training, with each session consisting of 960 repetitions of movement. Over the course of the entire training protocol, each subject completed 15,360 repetitions of movement on the MIT-Manus Shoulder-Elbow robot. If a patient was unable to maintain focus during a treatment session and could therefore only complete 640 repetitions during one sitting, their dosing could be modified to include 24 total sessions (3/week for 8 weeks, or 2/week for 12 weeks) to target the same total cumulative repetitions. Conversely, if an out of town patient was initiated for therapy and could only attend one time per week, but was able to complete a 2 hour session, their dosing could be modified to include 8 total sessions with 1,920 repetitions per session. This conceptual framework could be applied in many ways to accommodate patient needs while allowing the clinician to maintain evidence based practice.

It is important to note that there are countless other factors that must be considered in designing a rehabilitation plan for patients. No framework will be a one size fits all approach or address all compounding factors facing a patient. And, clinicians will rightly focus on more than rote, repetitious practice. Quality of movement, sequencing, functional gain, and dual-tasking are all aspects of recovery that clinicians strive to achieve. The Rehab Effort conceptual framework suggests a baseline level of practice, based on research findings that clinicians can strive towards while seeking motor recovery, and can incorporate additional aspects of practice concurrently or following achieving the targeted number of repetitions.

Considerations of "Random" Presentation

The lack of differentiation in performance amongst the participants in the blocked presentation group and random presentation group may be due to several potential factors. Motor learning literature suggests that a difference in outcomes between the two presentations should exist.[262] However, the manner in which random presentation was presented by the MIT-Manus Robot may have potential design limitations. By definition, blocked practice is the repetition of a single skill over and over. During blocked practice, variance in training is minimized while repetition is maximized. Learners participating in blocked practice "master" a skill before moving on to a new discrete skill.[263] In contrast, random practice engages learners in multiple skills in combination with each other, randomly working through trials of skill combinations and moving on to successive combinations with each trial building on the previous one.[263,264] The "random" element in this manner of learning engages the learner to be "on his or her toes" and prevents the learner from falling into a repetitive routine. Blocked practice is marked by low levels of cognitive interference, whereas random practice, by design, introduces cognitive interference.[265]

Potentially, the two presentation patterns introduced to subjects while participating in upper-extremity robotic-rehabilitation on the MIT-Manus robot failed to differentiate themselves as two distinct learning profiles. The visual representation of targets on the MIT-Manus robot consists of eight peripheral targets arranged in a clock-like pattern. In both the sequential and random presentation profiles, participants perform 80 repetitions of movement per "block" of intervention. Each target, regardless of learning profile, is touched by the subject ten times in each 80 repetition "block". During sequential training, the targets are illuminated in a clock-wise fashion, with no interruption in the sequence. Participants begin in the center of the array and first touch the 12 o'clock target. After they touch that target, they return to the center and then move on to the northeast target. This is repeated around the array until all 80 repetitions have been completed.

Within random presentation, the order in which participants touch each target is randomized. While each target will still be touched 10 times during the "block", the presentation order is non-sequential. On the surface, this is a random presentation of targets and does represent a random style of training. However, the properties of the task remain the same. The distance between targets is the same on each attempt and the visual properties of the training environment are unchanged. Additionally, there is no consequence of over-shooting a target or beginning to move in an incorrect direction. As a result, other than a non-sequential presentation of the targets, there is no appreciable cognitive distraction in the random training environment to differentiate it from the sequential intervention.

The absence of significant differences found in the movement time of children who participated in upper extremity robotic rehabilitation on the MIT-Manus robot with either a sequential or a random presentation of targets is therefore not surprising. Over the course of the entire intervention protocol, although movement times for both groups improved significantly from both pre-test to post-test and from pre-test to six-month follow-up, there was no significant difference between the two.

Despite the lack of an overall difference, there was significant variance between the two groups in the way they obtained their improved movement times. When comparing change scores for all one-way records over the course of the 16 treatment sessions, a significant difference was found in the change scores between the blocked and random group for one-way record 1 and one-way record 2. One-way record 3 also demonstrated a non-significant difference while one-way record 4 was more uniform. Participants in the blocked presentation group, on average, performed slightly better on the first one-way record each session than they had on the final one-way record the session before, indicating some level of consolidation (evolution of a skill into a more stable form that can result in improved performance in the future without continuous practice[254,266]) of the previous session's practice that was maintained. The blocked group then recorded slower movement times over the next 2 one-way records, suggesting that smaller gains were realized during the training of treatment blocks 1 and 2. They then experienced their largest average improvement in one-way record 4, indicating that the biggest gain in movement efficiency from training occurred during treatment block 3.

Conversely, participants in the random group experienced an average decline when comparing change scores of the first one-way record each day with the one-way record of the previous session. This indicates that, on average, participants in the random presentation group lost speed that that they had gained during the previous treatment session. Random group participants then consistently gained speed, decreasing their movement time, over each of the next three assessments each day.

That the two groups displayed such varied responses to the treatment protocol over the course of each treatment, yet improvements in both groups were nearly identical each day is interesting. The variation of training response does suggest that differentiation between the blocked and random training environments was present. The data utilized in this comparison was average change scores over all 16 treatment sessions. Potentially, the difference in results between the two groups may have been realized during different days of the training protocol. If so, this would suggest that children did respond differently to the blocked and random presentation at different points of the intervention duration, but that by the end of 16 weeks the outcomes normalized. If it is possible to identify these points of delineation through further analysis of the data, then protocols can be established that capitalize on the training effects of both the sequential and random target presentation. While the cumulative effects were equal, it may be that presentation style is more or less beneficial during different timeframes of recovery; and that a blocked or random presentation may have more utility earlier or later in treatment.

<u>Age</u>

Within the context of neuroplasticity, literature suggests that a child's brain may more readily undergo cortical reorganization than that of an adult. This is largely following the premise that all children, regardless of disability, are in a constant state of reorganization as they experience new stimuli and learn.[267] In healthy individuals, free of impairment, we may expect children to respond to new tasks more quickly than adults.

Within rehabilitation, this view is complicated by the introduction of novel tasks versus re-learning tasks that a patient had previously mastered. For children with CP, utilizing the MIT-Manus Shoulder Elbow robot to perform reaching tasks with their paretic upper extremity is a novel task. Depending upon the severity of their impairment, it is possible that these children had not previously used their upper extremity in a functional manner, outside of other therapies. Conversely, adults who experience a stroke and then participate in robotic training are working on movements and tasks previously mastered. The adult patient cognitively understands the activity, regardless of their ability to complete, whereas the pediatric patient may lack the appropriate reference. For both, their ability to learn, or re-learn, the reaching activity will be dependent on the ability of their brains to process and adapt to the learning stimuli and to overcome whatever obstacles are presented by secondary impairments of their injury, such as increased tone, decreased initiation, weakness, etc.

Given these considerations, our hypothesis relative to age in this study was that children in the middle of the age range would respond best to the robotic intervention. The age range of participants in the study was 4 to 11 years old, with an average age of 6.6 years. We hypothesized that children in the 6-8 year-old age range would respond better than those younger as they would have better attention and cognitive engagement in the task, and that being younger than those ages 9-11 would lend them to be more capable of cortical reorganization and improved performance as suggested by the literature.[215]

Following analysis, we found that in this study, age did not have a significant impact on the performance of children participating in the robotic intervention. (p = .582). There are several things to consider with this finding. First, participant age, at least that of children, may not contribute to the performance in the intervention. As designed, the intervention was simple enough for a four-year-old to complete, yet taxing enough to produce change in movement times across all ages in the study. This conclusion may be indicative of a need to introduce varying levels of cognitive demand to the interface of the robot, as older children may have experienced greater outcomes if challenged further.

Conversely, the sample size of the current study may not have been large enough to identify differences. Nearly half (10) of the 21 subjects enrolled in the study fell within the 6-8-year-old range. While that presented a good distribution for comparison, it may have been too low to identify differences. This distribution is also complicated by potential differences among the groups. The study had relatively good age homogeneity when dividing between presentation groups (blocked vs random), but that homogeneity decreased as the subjects were further stratified. For examples, when identifying age groups, an increased number of participants with a higher intake severity (Fugl-Meyer score) were found in the 6-8-year-old range which may have impacted improvement relative to the other groups.

Additionally, we have found that all participants significantly increased their movement speed from pre-test to post-test, and at follow-up. We have also found reason to suggest that the intervention may have benefited from additional repetitions as a larger proportion of day to day change was experienced during treatment block #3. Given a protocol that fully saturates a child's ability to improve daily, we may then see a differentiation in performance among age strata's.

Lastly, we must also consider that the age distribution in this study, regardless of confounding variables, is not wide enough to identify performance differences. As children develop and mature at different rates, there may be too much overlap in these defined groups to differentiate changes from one to another. Similar studies with adult patients post-stroke have also found movement times to decrease[15,30] and it would be appropriate to compare movement time changes to adult patients participating in an identical protocol to first determine that there is an affect by age.

Severity

For the purposes of this research study, severity was defined as the impairment of movement in the upper extremity as measured by the Fugl-Meyer assessment. Severity in this case does not necessarily define the nature of neurological impairment as the result of a child's diagnosis of CP, but rather the manifestation of that impairment through limitations in movement. The Fugl-Meyer is a standardized assessment that quantifies quality of movement through synergistic reaching activities. Synergy results from coordination of: strength, range of motion, motor control, and initiation to produce the required movement.

Within the outcomes assessments for the study, only the upper extremity portion of the Fugl-Meyer assessment was utilized. Further, in analysis, the upper extremity scores related directly to shoulder/elbow function where isolated to provide a more consistent representation of tasks that the Shoulder-Elbow robot was designed to address. It is possible that carry-over improvement to tasks not-related directly to the shoulder/elbow could be realized, but that was not the focus of this study. Isolating the shoulder-elbow components of the Fugl-Meyer left an available range of 0-25 for scoring. The intake scores (pre-test) for participants of this study ranged from 4 to 25, with the average shoulder/elbow Fugl-Meyer score being 12.4.

Our hypothesis was that children who were more severe at intake would experience greater gains in their movement speed over the course of training than those who were less severe at intake. The rationale behind this hypothesis was the assumption that there would be a ceiling effect on movement speed. Therefore, those who were more severe, and thus slower, initially would have more room to improve.

Upon analysis, the more severe group was slower during their initial one-way record (4.11s) than the less severe group (2.94s). Over the course of intervention, both groups improved their speeds significantly as compared to themselves, with the more severe group decreasing their movement time from 4.11s to 2.63s and the less severe group decreasing from 2.94s to 1.89s; but there was no significant difference between the two groups. Looking at this data from a pre-test, post-test perspective, it appears that the more severe group is demonstrating an increase rate of improvement. Based on this perspective, it could be hypothesized that additional visits would have allowed the more severe group to “catch up” with their less severe peers in movement time as their rate of decline in movement time is sharper.

However, looking at the day to day changes over the course of intervention for both groups demonstrated that the more severe group experienced a rapid improvement in movement time from day 1 (3.9s) through day 6 (2.54s), and then experienced a more leveled response to training over the final 10 treatment days that was nearly identical to the response demonstrated by the less severe group.

The original hypothesis to the effect of severity was false, as the more severe group did not improve their movement times significantly more than the less severe group, instead demonstrating statistically similar improvement. The results are encouraging though as the robotic intervention improved movement time in both groups. In that, the MIT-Manus Shoulder-Elbow robot did not discriminate. Regardless of functional ability at the onset of treatment, all participants could expect to improve their movement time. This finding is relevant to clinical application of the robotic device as there does not seem to be an issue of “responders” versus “non-responders”. While more severe patients may not achieve movement times equal to their less severe peers, they can expect a similar rate of improvement through training.

It could be concerning that both the more severe and less severe groups demonstrated a plateau effect in average movement time changes over each treatment day (following day 6). The case has been made that our intervention protocol would have potentially been strengthened by additional daily repetitions, and this could be dampening results here as well. But, while there is a plateau relative to early sessions, improvement remains throughout. With more understanding of children’s response to robotic interventions more sophisticated treatment programs will be developed. Robotics alone may be a suitable intervention for a specific duration of time early, with maximum benefit coming later through a combination of robotics and functional training.

Functional correlation of increased movement time

The value of any rehabilitation focus is its ability to assist the patient in improving his or her quality of life. Decreased movement time on the MIT-Manus Shoulder-Elbow robot, though indicative of improvements in motor control, initiation, strength, and others; is not necessarily correlated with increased functional ability by the participant. Anecdotally, we heard several examples from participants and parents of improved functional performance during, and following, the robotic intervention. These examples included: independently using a utensil with the paretic extremity to feed, improved donning/doffing of clothes, ability to manage clothes to allow independent toileting, and able to participate in video games with siblings. These are all examples of tremendous functional gains attributed to robotic training, but none have data to support.

Lacking in the robotic assessments is a functional component. For example, one of the best examples of an upper-extremity functional performance measures is the box and block assessment. The box and block assessment require participants to move blocks from one side of a treatment box, over a partition to the other side. The test is timed by the evaluator and has aged based norms for children ages 3 -10.[268] However, the test requires that participants grasp each block to move, a task not trained by the MIT-Manus Shoulder-Elbow robot. Performance on the box and block test then is not exactly representative of training on the robot, as performance may be hindered by the inability of the participant to achieve a grasp. Similarly, the nine hole peg test is another upper-extremity assessment that utilizes a speed component and has normative values for children[269] but also requires grasping to complete.

Self-report measures are another option to attempt to capitalize on functional improvements. The Pediatric Evaluation of Disability Inventory (PEDI) was indeed utilized in the original study from which this data was derived. We found an 8 point reported improvement for all groups from pre-test to post-test that was maintained at follow-up, though the results were not significant.[29] Self-reports such as the PEDI are useful for gathering higher-level views of the success of the intervention, but do not allow researchers to identify specific measures or trends. Self-reports are also more susceptible to error and can skew subjective in nature.

It may then be that robotic generated data cannot be directly correlated with functional improvements and that a combination of both kinematic data and functional reporting is required to fully assess the effectiveness of a robotic intervention. Regardless of the documentation of functional improvement, a subject's improved kinematics demonstrate changes during robotic training. The carry-over to functional tasks may require the inclusion of additional training parameters, instituted outside of the robot to fully maximize the capabilities of advanced technology.

<u>Limitations</u>

This secondary analysis has several limitations. First, the population utilized in the study was small. The group recruited (n = 21) was adequately sized to allow for strong analysis from an overall perspective, but lost power when further stratified into smaller groups for comparison, i.e. target presentation, age, severity. Additionally, 5 subjects were lost to follow-up after completion of the post-test assessments which further limited the power of the follow-up assessments.

Additional limitations have been identified following the secondary analysis. The study protocol was for each participant to complete 960 repetitions of active robotic training in each of 16 treatment days. Analysis of the average change scores between each block of treatment suggests that additional repetitions of training were warranted. If true, this shortcoming in the protocol may have potentially altered the results of the other comparisons as well, namely the plateau effect as was discussed relative to severity.

The original study was primarily focused on examining the differences between a blocked presentation of targets and a random presentation of targets. As has been discussed, a potential limitation of the robotic device itself may have been its inability to adequately distinguish blocked from random presentation. Although differences in response to the two presentations did present themselves, the overall lack of effect suggests that the two training environments were similar.

Future Study Considerations

The utilization of kinematic data derived from the MIT-Manus Shoulder-Elbow robot presents many available and needed avenues for future study, not just for the MIT-Manus but for robotic interventions in general.

Immediately, from this data set alone, there remains untouched kinematic data that can be analyzed for additional inquiry into the application of the MIT-Manus Shoulder-Elbow robot for children with hemiplegic CP. For example, further analysis of discrete movement units within individual reaching attempts may give a more detailed, objective description of the improvement in coordination or muscle synergy that occurred during robotic training. Time to peak velocity or time to peak acceleration may provide insights into initiation and cognitive attentiveness, whereas path length may allow for conclusions regarding motor planning. Additionally, kinematic assessment of the circle data produced during this study may enable researchers to draw more concrete conclusions regarding the amount of learning that occurred relative to the improvement attributed to a training effect. From this data set alone, several more studies can be conducted that will provide a better understanding of children's response to this particular robotic intervention protocol.

Moving forward, there were several questions left unanswered from this study that warrant further investigation. Our data suggests that additional repetitions, perhaps in the form of a fourth training block, may have produced better outcomes for our subjects. Utilizing the power of the kinematic data derived from robotics, research should be done to determine where the point of diminishing returns exists for children. If robotics are to be included in clinical protocols as part of a patient's rehabilitation program, clinicians must know the parameters of which to apply this technology. Falling short of the number of repetitions best suited to provide lasting change will be a disservice to patients.

Within the idea of additional repetitions of robotic training, there is a clear need to determine the appropriate inclusion of functional training to complement the gains realized by robotics alone. The adage exists that "Practice makes Perfect", or, more precisely, "Perfect Practice makes Permanent". In following this, we must train patients in the activities that they are to perform. Robotics may provide the best option to begin patients on the path towards functional recovery, but they cannot be the end. Clinicians must incorporate functional, task-specific training in order to realize functional improvements. It is imperative that we identify the appropriate points along the recovery continuum to combine functional training with robotic interventions.

Lastly, based on motor learning theory, it is known that there are specific benefits to both blocked and random practice in both skill acquisition and motor recovery. While the overall results of our study did not find a difference between the two target presentation groups, the within-session average change scores suggested a different learning rate for the two groups. Future research should focus on differentiating the two target presentations to capitalize on the benefits of each type of learning. Then, studies to examine to proper sequence of incorporating each presentation type into robotic training should be completed.

The culmination of these future studies, along with results of studies previously completed, should provide a more complete guide to the formation of a robotic-based protocol for motor recovery in children with hemiplegic CP that combines motor learning, proper dosage, and functional carry-over to achieve the greatest clinical results possible.

Chapter 6 : Conclusion

This secondary analysis utilized kinematic data of children with hemiplegic cerebral palsy (CP) collected from the MIT-Manus Shoulder-Elbow robot to investigate the motor learning changes occurring during this novel training. Results from this analysis indicate that upper extremity robotic rehabilitation, particularly when utilizing the MIT-Manus Shoulder-Elbow robot, is a viable option for improving motor performance amongst children with CP. Previous literature has supported the use of upper extremity robotic rehabilitation in both the adult post-stroke population[11,21,114], as well as in the pediatric CP population[40,44]. The aims of this secondary analysis where to validate the clinical findings of the original study through kinematic assessment and to explore the learning changes that occurred both within and between sessions.

Most notably, this analysis suggests that robots are indeed a beneficial treatment option for improving motor function in children with CP. When looking at movement times of all subjects during one-way records, a significant decrease was found pre-test to post-test and remained significant at follow-up. Within that, there was no discrimination by the robot to any of the various sub-groups within the study; similar improvement was observed for all groups, regardless of age, intake severity, or group placement. This finding was particularly notable as it suggests that all patients suitable for treatment on the MIT-Manus robot can expect to experience some degree of improvement.

The central question to the original study design was investigating the difference in children's response to treatment when they were presented with a training environment that was either sequential or random in target presentation. Like the original study, the secondary analysis found no significant difference in outcomes within these two groups.

However, our data did suggest that though the two presentation groups improved similarly overall, there was enough variation in the two target presentations that learning occurred at different rates, though ultimately ending at the same level of improvement.

Despite the original hypothesis to the contrary, this study also found that children improved with increased repetitions of training. When comparing the three blocks of robotic training that children participated in each day, the greatest amount of improvement was realized during the third and final block of treatment. This finding suggests that there was not a saturation point during treatment and that children may have even benefited from more repetitions than the 1,024 in this study. Additionally, we found that over the course of treatment sessions, there was no plateau in improvement; children were steadily improving movement time throughout the 16 sessions, suggesting that more sessions may have been beneficial.

The MIT-Manus robot proved to be more discriminatory in assessing changes in motor function than that of traditional clinical measures. Future research studies of robotic rehabilitation should utilize this characteristic to examine application and dosing within both the pediatric CP population and others. The ability to identify trends within treatment will allow for more comprehensive and timely discovery. The findings of this study present an opportunity to explore motor learning in future studies with increased repetitions and treatment sessions to optimize the delivery of robotic rehabilitation and to maximize its efficacy.

As evidenced by this secondary analysis, what we thought was an incredible amount of repetitions, 1,024 per session, was enough to produce change, but still not enough to saturate motor learning in children with hemiplegic CP. Previous research has laid out the framework in both healthy human motor learning and animal models[86,90,92,106,261] for intensity of training to achieve cortical change. Lagging has been the translation of that knowledge into the clinical setting. Future research and clinical implementation through the lens of the Rehab Effort conceptual framework, as has been introduced here, offers the opportunity to move towards more intensive treatment delivery to capitalize on motor recovery. Rehabilitation Robotics has potential to be the medium of training that allows patients with neurological impairment to reach the level of effort required to induce cortical change and long-lasting functional improvement.

Appendix A

Pre-screening: Evaluation

**Can be completed via chart review/phone conversation. Please gather basic patient information to determine if patient is potentially eligible for inclusion into study. Additional testing will be required during initial pre-test to determine ultimate eligibility.*

Date: _______________ Evaluator: ___________________________

Subject Identification

ID: ________

Subject Name: _______________________ Date of Birth: ________________________

Gender: Male/Female (circle) Age: _____________

Parent/Caretaker Name: ____

Home Address: ____

Contact Phone Number: ____________________________

History

Primary Diagnosis: ____

Secondary Diagnoses: ____

Surgical History: ____

Spasticity Management: ____

Current Therapies

Physical Therapy / Occupational Therapy / Speech Therapy (circle)

Frequency of Current Therapies: ____

Location of Current Therapies: ____

Eligibility Checklist

Is Subject between the ages of 3 and 16 years?	Yes / No
Was diagnosis of CP or ABI given 6 months prior to inclusion in study?	Yes / No
Does subject present with Upper Limb hemiplegia?	Yes / No
Is subject able to follow simple verbal commands?	Yes / No
Is subject able to remain seated for 40-60 minutes?	Yes / No
Does subject currently play and/or show an interest in video games?	Yes / No
Is subject willing and able to maintain attendance and commit necessary time to study?	Yes / No

**If YES to all, subject may be referred to schedule pre-testing with study evaluator. Subject will need to schedule two pre-test sessions. Scheduling should be done by calling:* [redacted]

Appendix B

IUPUI/CLARIAN INSTITUTIONAL REVIEW BOARD (IRB) REVIEW

DOCUMENTATION OF REVIEW AND APPROVAL (DRA)

IRB STUDY NUMBER: 0911-65
(IRB Office will assign)

Please type only in the gray boxes. To mark a box as checked, double-click the box, select "checked", and click "OK".

SECTION I: INVESTIGATOR INFORMATION

Principal Investigator: **Dierks, Tracy, A.** **Department:** **Physical Therapy**
(Last, First, Middle Initial——must have faculty/staff status or faculty sponsor must sign)

Building/Room No.: Coleman Hall 326 Phone: [redacted] E-Mail: [redacted]

Contact Information:

Name: Tracy A. Dierks Address: Coleman Hall 326 Phone: [redacted]

Fax: [redacted] E-Mail: [redacted]

If this is a Student Protocol, List Name of the Student: Phone:

Protocol Title: **Robot-Mediated Task-specific Training in Cerebral Pasly: Block versus Random Presentation**

Sponsor/Funding Agency: Cerebral Palsy International Research Foundation PI on Grant: Greg Wilson, MD

Sponsor Protocol #/Grant #: R-794-09 Period: From: Jan. 2010 to Jan. 2012

Sponsor Type: ☐ Federal ☐ State ☐ Industry
☒ Not-for-Profit ☐ Unfunded ☐ Internally Funded

Grant Title (if different from project title):

SECTION II: TYPE OF REVIEW

☒ Expedited Review
☐ Full Board Review (*Choose One*) → ☐ Behavioral or Social Sciences (IRB-01)
☐ Biomedical (*Choose One*) → ☐ IRB-02 ☐ IRB-03 ☐ IRB-04 ☐ IRB-05

SECTION III: SPECIAL SUBJECT POPULATIONS INVOLVED IN THE RESEARCH

☒ Children
☐ Cognitively Impaired
☐ Economically/ Educationally Disadvantaged
☐ Human Fetuses (or Fetal Tissue) or Neonates
☐ Pregnant Women
☐ Prisoners

SECTION IV: DOCUMENTS INCLUDED WITH RESEARCH SUBMISSION

☒ Informed Consent Document(s), dated:
# of consent documents: 1
☒ Expedited Research Checklist, dated:
☐ Recruitment Checklist, dated:
☐ Advertisement(s), dated:
☐ Drug Brochure/Packet Insert, dated:
☒ Assent Document(s), dated:
# of assent documents: 1
☒ Summary Safeguard Statement (SSS), dated:
☐ Authorization(s), dated:
☒ Protocol, dated:
☒ Other, description: Request form for the inclusion of children in research

You only need to list document dates if they are required by the investigator or sponsor.

Recorded in the Minutes of:

1

v03/01/09

SECTION V: INVESTIGATOR STATEMENT OF COMPLIANCE

By submitting this form, the Principal Investigator assures the Board that all procedures performed under the project will be conducted in strict accordance with those federal regulations, University and Clarian Health Partners policies that govern research involving human subjects. He/she acknowledges that he/she havs the resources required to conduct research in a way that will protect the rights and welfare of participants. He/she agrees to submit *any* deviation from the project (e.g. change in principal investigator, research methodology, subject recruitment procedures, etc.) to the Board in the form of an amendment for IRB approval prior to implementation.

SECTION VI: IRB APPROVAL

This research project, including all documents included with the submission (e.g., informed consent statement, authorization, and/or waiver of authorization) has been reviewed and approved by the Indiana University-Purdue University Indianapolis Institutional Review Board or the Clarian Institutional Review Board for a maximum of a one year period beyond the final approval date unless otherwise indicated as follows:

Authorized IRB Signature: [redacted] IRB Approval Date: 12/7/09

DEC 7 2009

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Curriculum Vitae

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Education

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Professional and Other Experience

2016 – Present	Guest Lecturer, University of Bellermine Physical Therapy Department
2013 – Present	Guest Lecturer, University of Indianapolis Krannert School of Physical Therapy
2012 – Present	American Physical Therapy Association Task Force: FiRST Initiative
2006—Present	American Physical Therapy Association Member (Pediatric, Neurology and Research Sections)
2010—2012	Board Member, Indiana Chapter APTA- Central District
2010—2015	Professional Mentor, Butler University Health Services
2010—2014	Guest Lecturer. Butler University Health Sciences
2008—2012	Board of Directors, IU School of Health & Rehab Sciences- Alumni Assoc.

Honors

2011	Anita Slominski Caring Award, United Cerebral Palsy Association of Greater Indiana
2011	Indianapolis Rising Star, *The Indianapolis Star*

Selected peer-reviewed publications

1. Ladenheim B, Altenburger P, **Cardinal R**, Mast J, Monterroso L, Dierks T, Krebs HI. The effect of random or sequential presentation of targets during robot-assisted therapy on children. *NeuroRehabilitation*. 2013; 33: 25-31.
2. Dierks T, Phipps R, **Cardinal R**, Altenburger P. The effect of hip muscle strengthening on pain and running mechanics in females with patellofemoral pain. *Medicine & Science in Sports & Exercise*. 2011; 45(3): 93.
3. Warden SJ, Fuchs RK, Kessler CK, Avin KG, **Cardinal R** and Stewart RL: Ultrasound produced by a conventional therapeutic ultrasound unit accelerates fracture repair. *Physical Therapy.* 2006; 86(8):1118-27.

Additional Publications

1. Altenburger P, Pilutti L, Motl R, **Cardinal R**, Savanur D, Frame J. End-Effector Robotic Rehabilitation in Progressive Multiple Sclerosis: A Multiple Case Report. Multiple Sclerosis Alliance International Conference. Toronto, Ont. 2018.
2. Gangwani P, **Cardinal R**. Use of Robotic Assisted Gait training in a patient with Hemiplegic Cerebral Palsy. American Physical Therapy Association Combined Section Meeting. New Orleans, LA. 2018.
3. Massie C, Reutman R, Lybarger H, Schafer E, Zheng D, **Cardinal R**, Altenburger P. Clinical Implementation of Upper-Extremity Rehabilitation Robotics. Program 1022. American Occupational Therapy Association Annual Meeting. Salt Lake City, UT. 2018.
4. Alotaibi M, **Cardinal R**, Bridgeman K, Fuller E, Altenburger P. Robot-Assisted, Task-Specific Ankle Training to Improve Motor Function in Children with Cerebral Palsy. APTA Academy of Pediatrics Annual Meeting. Cincinnati, OH. 2017.
5. Christensen K, Hart A, Jay K, Larson C, Tellus S, Stanley S, Kraus S, Wichlinski R, Wilson M, Nobbe J, Goldsbury C, Massie C, **Cardinal R**, Altenburger P. Comparing Clinical Use and Published Trends in Robot-Assisted Gait Training. Indiana APTA Fall Conference. Indianapolis, IN. 2017.
6. Kerr L, **Cardinal R**, Prewitt C, Athanasakes J. Promoting patient access to rehabilitative technology through utilization design. American Congress of Rehabilitation Medicine. Chicago, IL 2016.
7. Scheidler C, Zambon K, Mathews C, Zehr A, Sigmund S, Denning N, **Cardinal R**, Altenburger P. The influence of training environment on self-selected gait speed. American Physical Therapy Association Combined Sections Meeting. Anaheim, CA 2016.
8. Alotaibi M, **Cardinal R**, Altenburger P. The Effectiveness of Anklebot in Reducing Motor Impairment and Improving Motor Function for Children with Cerebral Palsy (CP). Indiana University School of Health and Rehabilitation Sciences Research Summit. Indianapolis, IN 2015.
9. Deepak Rajendra S, **Cardinal R**. Exploring Robotic-Assisted Locomotor Training in Physical Therapy with Multiple Sclerosis. National Multiple Sclerosis Society Annual Conference. Indianapolis, IN 2015.
10. Altenburger P, **Cardinal R**, Fuchs R, Gleason S, Cappel M. Creating a robotic-based intervention paradigm that impacts a child’s daily physical activity levels by improving locomotor capacity. American Academy of Cerebral Palsy and Developmental Medicine Annual Conference. San Diego, CA 2014.
11. **Cardinal R**, Gleason S, Cappel M, Fuchs R, Altenburger P. Robotic-assisted locomotor training for a four-year-old child with Cerebral Palsy emphasizing intensity and cognitive engagement. American Physical Therapy Association Combined Sections Meeting. Las Vegas, NV 2014.
12. **Cardinal R**, Altenburger PA, Krebs H, Dierks T. Robotic task-specific training of the upper extremity in children with Cerebral Palsy. American Physical Therapy Association Combined Sections Meeting. Chicago, IL 2012.

Peer-Reviewed Presentations

1. **Cardinal R**, Massie C, Altenburger P. Kinematics to assess learning changes during robotic rehabilitation in children with hemiplegic cerebral palsy. American Academy of Cerebral Palsy and Developmental Medicine Annual Conference. Montreal, QE. 2017
2. Majsak M, Mast J, Monterroso L, Altenburger P, **Cardinal R**, Aisen M, Wolcott C, Krebs H. Relationships between the dosage of robot-assisted upper limb therapy, outcomes in body function and activity, and the individual characteristics of children with cerebral palsy: a multi-center case series. American Academy of Cerebral Palsy and Developmental Medicine Annual Conference. Austin, TX 2015.

Invited Presentations

1. Frame J, **Cardinal R**. Motion and Gait Analysis: Driving Innovative Robotic Based Therapy and Research. Gait and Clinical Movement Analysis Society Annual Meeting. Indianapolis, IN 2018.
2. **Cardinal R**. Rehabilitation Robotics in TBI. Traumatic Brain Injury Cases, Indiana Continuing Legal Education Forum. Indianapolis, IN 2017.
3. **Cardinal R**. Rehabilitation Robotics: Innovative Evidence-Based Practice. Indiana University School of Health and Rehabilitation Sciences Inter-Professional Education and Practice Conference. Indianapolis, IN 2017.
4. **Cardinal R**. Panel Member- Advancements in the Medical Products “Space”. Indiana Life Sciences Collaboration Conference Series. Indianapolis, IN 2016.
5. **Cardinal R**. Innovative robotic based therapies. Acute Care in Neurotrauma Symposium, Indiana University Health. Indianapolis, IN 2014.
6. **Cardinal R.** Robotic Therapy for kids: theoretical and practical applications driving the use of robotic-assisted therapies in rehabilitation. AHDI Annual Convention and Exposition. Indianapolis, IN 2012.

Selected Interviews/Media Publications

2015	Interview: “NeuroHope: Taking a Stand”. *Indianapolis Monthly*. November, 2015.
2013	Interview: “A Deep Dive into the Brain”. *U.S. News & World Report, Best Hospitals Edition*.
2012	Interview: “Visions of Science, Technology, and Physical Therapy”. *PT InMotion*. June, 2012.
2012	Featured Article: “This is Why: Happy Machinations” *PT InMotion*. March, 2012.